Exclusive On-Line Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Achieving Six Sigma Quality in Medical Device Manufacturing by Use of Design of Experiments and Statistical Process Control

by Per Vase

This article highlights how a manufacturer of medical devices obtained Six Sigma quality in production by the use of Design of Experiments (DoE) and Statistical Process Control (SPC) and discusses how these tools can be an important step toward the Future Desired State.

Introduction

A major healthcare company wanted to introduce an ultrasonic welding technique for making a critical component for one of their new medical devices. A failure in a welding would have serious consequences for the customer. The Acceptable Quality Level (AQL) was a sub-ppm error rate since millions of weldings have to be made each year. Such a low AQL can not be ensured by a traditional offline QC sampling inspection. Instead, a lean production layout was needed. All welded components should be monitored for welding quality in-line at production speed. Bad parts should be sorted out automatically by the welding equipment. To ensure on-target quality and high yield, the monitoring of welding quality should be used to control the process from Statistical Process Control (SPC) charts. Prior to the implementation of SPC, Design of Experiments (DoE) was used to correlate Critical To Quality (CTQ) attributes to parameters that can be measured quickly and non-destructively on all samples to obtain timely measurements. In addition, DoE has been used to establish the correlation between process result and process settings, the so called transfer function. By using the transfer function, it is possible not only to monitor, but also adjust the process and control manufacturing to ensure final product quality. Finally, DoE has been used to establish the Design Space. Data is quickly, conveniently, and visually displayed using SPC charts on monitors as immediate operator information and stored in a database for trend analysis over a longer period of time. By using the SPC system, Six Sigma quality has been obtained.

A general description of the Six Sigma tools used and methodology employed is presented, including how they can be of value for the pharmaceutical industry.

Background

The FDA defines in their Guidance for Industry[1] Process Analytical Technology (PAT) as: "The Agency considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final

Table A. Typical Six Sigma training.

% of organization	Training Subjects	Training Duration	Roles
100	How to read a control chart and a capability index	1 day	Act on control charts
10	How to perform a DoE, create a control chart, and select the right capability index	2 weeks	Green Belts. Project participant in DoE and SPC projects with supervision
1	How to manage projects using DoE and SPC	4 weeks + project	Black Belts. Project Manager. Supervisor.

product quality." Tools for controlling manufacturing from measurements of CTQ parameters have been available for more than 80 years since W.A. Shewhart in 1924 introduced the control chart concept in Bell Laboratories. Although frequently used in some industries (e.g., the automotive industry), control charts have never obtained as widespread use as they deserve, and especially within the pharmaceutical industry they are rarely used. There are several reasons for this. Three of the main reasons why control charts have never previously made the breakthrough within the pharmaceutical industry are:

1. no urgent need for change
2. lack of operational process understanding before implementing SPC
3. implementation attempt by statisticians instead of end users

No Urgent Need for Change

The pharmaceutical industry has for many years been in a special environment with strong regulation and patent protection. Production efficiency and yields have not, as in many other industries, been the major competition parameter. As a result of this, pharmaceutical manufacturing has a low manufacturing performance compared to other industries.[2,3] A famous article in The Wall Street Journal expressed it this way: "pharmaceutical manufacturing techniques lag far behind those of potato-chip and laundry-soap makers."[2] In order to avoid defective products reaching the market, heavy Quality Assurance (QA) and Quality Control (QC) strategies have been established. A recent study by IBM[3] shows that pharmaceutical manufacturing typically has a process sigma level of 2.5 in productions, corresponding to a C_p of 0.83 or 150000 ppm defects. In comparison, pharmaceutical release has a quality sigma level of 5 corresponding to a C_p of 1.67 or 200 ppm defects. No other industry has this three orders of magnitude defect difference between produced quality and released quality. It is the result of an incredible effort in QA and QC, especially in end-product testing and sorting, leading to Quality by Inspection. This is done to absolute perfection and there is not more to gain following this route. However, there are two drawbacks to this working practice:

1. It drives the prices up, due to high Costs of Poor Quality (CoPQ).
2. It makes it impossible to improve the released quality even further.

As it is said in the FDA PAT Guidance, "The health of our citizens depends on the availability of safe, effective, and affordable medicines." The pharmaceutical industry has to find a more efficient way of controlling manufacturing processes to make medicines affordable for a larger group of customers. In addition, the quality needs to be improved further; 200 ppm is not good enough for critical characteristics. The industry can not continue to increase the QC efforts by even larger sample sizes in end product testing; the limit is reached!

This general industry trend also can be seen in the latest ISO sampling standard,[4] which moves away from traditional AQL sampling methods and recommends screening (continuous monitoring) and process control instead for critical characteristics. This issue also is highlighted in a recent publica-

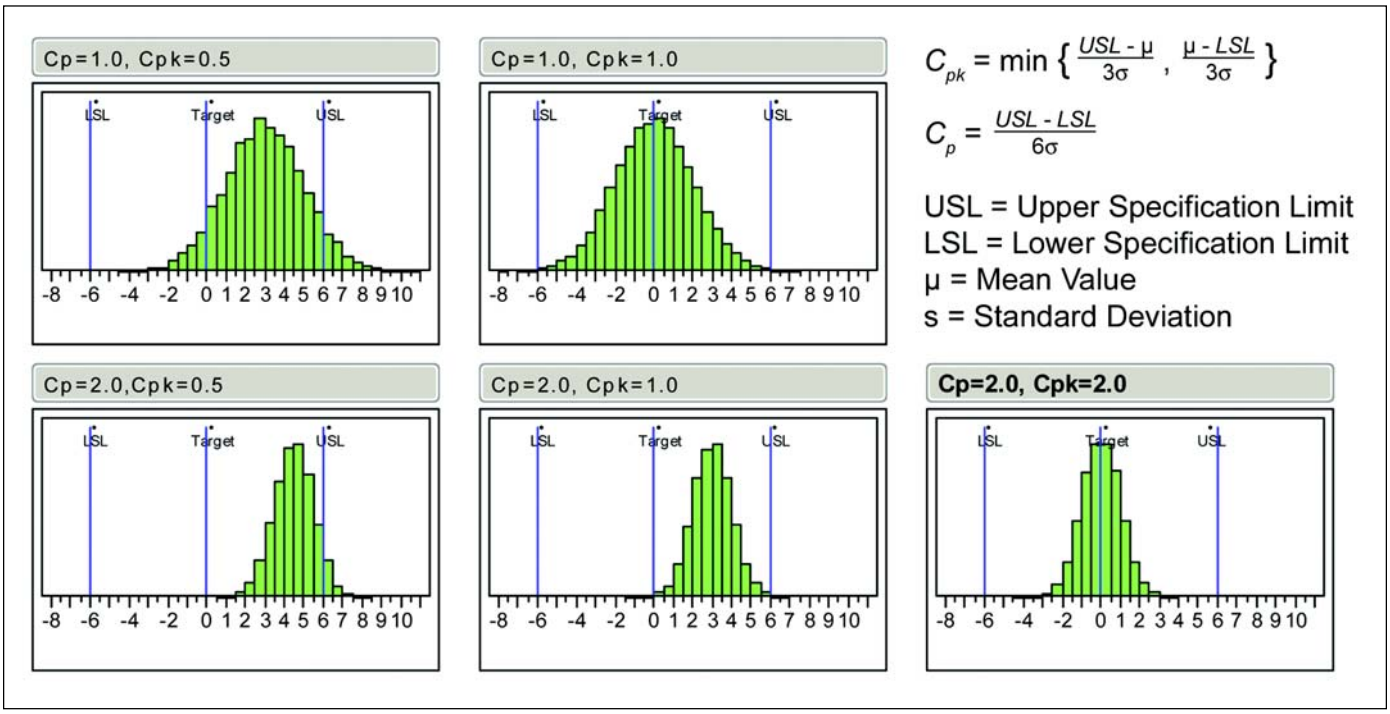


Figure 1. Illustration of Capability index C_p and C_{pk}.

Sigma Level	Yield %	C_p before Sorting	System Downtime each year (days)	CoPQ % of Sales (8)	CoPQ % of Sales (9)	
1	30	0.33	255	> 40	> 70	Non competitive
2	69	0.67	112	30-40	> 40	Non competitive
3	93	1.00	24	20-30	25-40	Average Pharma Sigma = 5 after sorting (3)
4	99.4	1.33	2,27	15-20	15-25	Average Other Industries
5	99.98	1.67	0.085	10-15	5-15	
6	100	2.00	0.0012	< 10	< 1	World Class Pharma (3) Automotive Industry
7	100	2.33	0.000069	?	?	
8	100	2.67	0	?	?	Semiconductor Industry

Table B. Relation between Sigma Level and Cost of Poor Quality. Sigma Level is the number of standard deviations between target value and specification limits.

tion from the FDA[5] inspired by recent Military Standards.[6]

There is now an urgent need to change that had not been recognized previously.

Lack of Operational Process Understanding Before Implementing SPC

Many SPC implementations have failed due to lack of operational process understanding. In order to be able to establish a proper control strategy, processes need to be understood, to know which parameter to measure and plot in a control chart, and when there are points out of control to know what to do about it. As it is written in the FDA PAT Guidance for Industry:[1]

"A process is generally considered well understood when:

1. all critical sources of variability are identified and explained

2. variability is managed by the process"

If it is not known how to act on points out of control on the chart, the control chart only creates panic, not improved processing. Of course there will be process understanding based on learning by doing in all companies. However, this is very person dependent and typically people act differently on process measurements. The understanding is not operational, it is subjective. With subjective process understanding, control and adjustment often make things worse compared to not doing anything. This has resulted in the typical "don't change anything after PQ strategy," strong change control, and the belief that if it worked in PQ, it will work at all times disregarding e.g., equipment wear, raw material variation, and climatic changes. Running three PQ batches with minimum variation between them, just after each other, heavily monitored by process experts and engineers (who will not be there in normal production) does not solve this issue.

Fortunately, the tool is there to obtain process understanding and test if processes are robust: DoE. Again, this is a more than 80 year old tool originally developed by R.A. Fisher in 1922. By systematically varying all factors of interest in a DoE, it is possible with a minimum number of experiments to create operational process understanding that can be shared within the whole organization. When this process understanding is established in the organization, the risk is minimized for the customer and for the company. Risk is inversely proportional to understanding. It will be known how to control and adjust processes in order to manage variation in process conditions going away from the "don't change anything" strategy. Process understanding also will lead to a more lean regulatory approach. It is written in the guidance:[1] "For processes that are well understood, opportunities exist to develop less restrictive regulatory approaches to manage change."

Implementation Attempt by Statisticians Instead of Users

Most pharmaceutical companies above a certain size have a statistical department that takes care of analyzing results of clinical testing, input to product registration, and dimensioning sampling plans for end product testing and release. For these companies, it has been obvious to try to use these statistical departments for implementing DoE and SPC in manufacturing. However, this has often resulted in procedures that are too complex, reports that no one outside the

Figure 2. Cost of Poor Quality Iceberg. Cost of Poor Quality is much more than the direct costs.

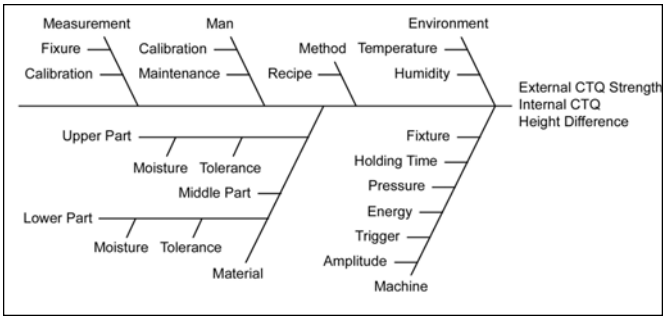


Figure 3. Ishikawa cause and effect diagram.

statistical department could understand, too slow response to production needs, perfectly analyzed DoE's with the wrong factors tested, and SPC on wrong parameters. Other industries overcame these challenges in the 1990s by implementing Six Sigma, originally developed by Motorola. A very important part of Six Sigma is not to use statisticians to perform and implement DoE and SPC. Statisticians shall be used to train the organization in these methods so they can do it themselves. This ensures test of the right factors in DoEs, process experience used in the analysis phase, and it ends with control strategies that can be used on the shopfloor. This requires an extensive training program where the whole organization is trained in applied statistics to different levels as shown in Table A.

Previously, intensive training was needed to be able to perform DoE and SPC, but with today's statistical software tools, it is possible to be operational after a few weeks of training especially with guidance from statistical experts.

Cost of Poor Quality

Cost is the driving force behind most decisions. In order to get management attention to implement DoE and SPC, the implementers need to be able to address the cost savings from using the tools. It is obvious to get inspiration from the work done during implementation of Six Sigma. A Six Sigma project will typically minimize variation and drive sigma level and capability index C_p up. Six Sigma projects are always cost/benefit driven. Models for the relation between Cost of Poor Quality (CoPQ) and sigma level and/or C_p have been developed. Before proceeding, C_p and sigma level will be defined. Figure 1 shows the formulas for and a schematic of the capability index C_p and C_{pk}. Sigma σ represents the standard deviation of the distribution of measured data. C_p is the ratio between tolerance window and process width (6σ). A C_p of 1 corresponds to the width of the tolerance window is equal to the width of the process (i.e., the process width exactly fits the tolerance window). This does not allow any drift of the process; it needs to be on target at all times. Having a C_p of 1 there is room for +/- 3σ within the tolerance window, which is called sigma level 3. In order to allow for drift, C_p needs to be higher than 1. When C_p=2, there is room for +/- 6σ within tolerance window, called sigma level 6 or Six Sigma Quality. Often, an analogy is made to driving a car into a garage. The tolerance window is the width of the garage and 6σ corresponds to the width of the car. In order to ensure that any driver will never hit the edges of the garage, the width of it has to be twice the width of the car, corresponding to a C_p=2.

The C_p index alone is not enough to describe the process. It is possible to have a high C_p and a low yield if the process

Numberof Steps	C_p=1,00 3 sigma	C_p=1,33 4 sigma	C_p=1,67 5 sigma	C_p=2,00 6 sigma
1	66807	6210	233	3
2	129151	12381	465	7
3	187330	18514	698	10
4	241622	24608	930	14
5	292287	30665	1163	17
6	339568	36684	1395	20
7	383689	42666	1627	24
8	424863	48[illegible]	1860	27
9	463287	[illegible]4519	2092	31
10	499143	60390	2324	34
20	749142	117133	4642	68
50	968481	267617	11565	170
100	999007	463615	22997	340
1000	1000000	998029	207574	3392

Lean

Lean Six Sigma

Six Sigma

Table C. Relation between ppm error rates, number of process steps, and C_p for each step.

is far away from target as illustrated in the lower left corner of Figure 1. To solve this issue, another supplementary index: minimum capability index C_{pk} is used. It is the distance from the mean value to the nearest specification limit divided by 3σ (half process width). If the process is on target, $C_{pk}=C_p$; if the process is not on target, $C_{pk}<C_p$.

Capability indices C_p and C_{pk} are excellent key performance indices to describe a process. However, they shall be used with care. They are calculated on the assumptions that the process is in statistical control and data are normal distributed. This is often not the case and other types of indices (e.g., P_p and P_{pk}) should be used as described in a recent ISO standard.[7]

The capability index is used as a parameter in the cost models correlating C_p and CoPQ measured in percentage of sales as shown in Table B. The CoPQ numbers for lower sigma levels might seem very high. This is due to CoPQ calculations that take into account all contributions to Cost of Poor and not just the tip of the iceberg[10] as shown in Figure 2. In addition, the yield column in Table B is for one process. Typically, many processes or components need to work at the same time to have a successful product so the yield of the product is lower than the yields of the individual processes as shown in Table C. By applying lean (reducing the number of steps) and Six Sigma (improve Quality of steps), low error rates of 3 ppm can be obtained.

Design of Experiments (DoE)

The first step in a DoE is to define the response variables (i.e., what is to be measured on the runs in the experiment to distinguish between good and bad runs). Typically, external (seen from the customer) CTQ parameters will be measured together with internal (measured quickly, non-destructively, and correlating with external) CTQ parameters. An important part of a DoE is to correlate internal to external CTQ parameters. The next step is to identify the factors that are expected to influence the responses and will be varied in the experiment. This could be done in a process review.[11] Typically, the list of factors is too long to be able to make a precise mathematical function relating the factors to the responses in one reasonably sized experiment. It is normal to start with a screening experiment where the many factors are varied in two levels only and assuming no interactions to keep the number of runs low. The purpose of this experiment is not to make the mathematical model, but only to find the factors that has the largest influence and requires a more detailed investigation. This step will typically cut the number of factors down to a level where they can be coped within a single model experiment. This model experiment, called a response surface experiment, establishes the precise mathematical relationship between factors and responses, including non-linearities. An important output of the DoE is the Design Space: "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality."[12]

Statistical Process Control (SPC)

To ensure continuous optimized performance, processes need to be controlled during production to adjust for, e.g., raw material differences, equipment wear, and environmental changes. From the DoE results, the external CTQ's can be predicted by measuring the internal CTQ. If the level of internal CTQ changes, the process can, based on the DoE results, be adjusted to change level. However, two questions remain to be answered:

1. How big shall the change in internal CTQ be before the process parameters are adjusted?

2. Which process parameter shall be used to adjust the process?

Two types of variation exist: random variation and systematic variation. Random variation is characterized by being unpredictable and having no assignable cause (or a sum of many small contributions, where it is practically impossible to assign causes). If it is tried to adjust on random variation, it will only make the variation larger. If the internal CTQ increases due to random variation, it does not mean that the level has actually changed and if the level is adjusted down based on this, variation is added. Systematic variation is characterized by having an assignable cause behind the change and the process can be back on track by either removing the assignable cause or compensate the assignable cause by adjusting process parameters. So in short, the operator shall act on a change in CTQ if it is due to systematic variation and leave the process as is if it's due to random variation. The obvious question now is how will the operator know? The answer is straightforward: use SPC. Basically, SPC distinguishes between random and systematic variation. When control charting, the measurements are typically divided in two subgroups and the mean and range (maximum-minimum) are plotted versus time. Based on the variation within a subgroup, control limits can be calculated for both the mean and the range. When new mean values are within the control limits the process is only subjected to random variation and process adjustment will only increase variation. If it is outside the control limits, there is an assignable cause that either should be removed or compensated by adjustment. From the DoE, it will be known which process parameter is optimal for adjustment.

DoE and SPC Case Study

Train Staff

In order to ensure that the use of DoE and SPC resulted in something that could be used on the shop floor, an intensive training program was initiated as shown in Table A. All employees were given a one day course in SPC, including capability indices and how to act on a control chart. Ten percent of the employees were trained in using DoE and SPC, including training in the selected statistical software. The training was a part of the general lean implementation at the

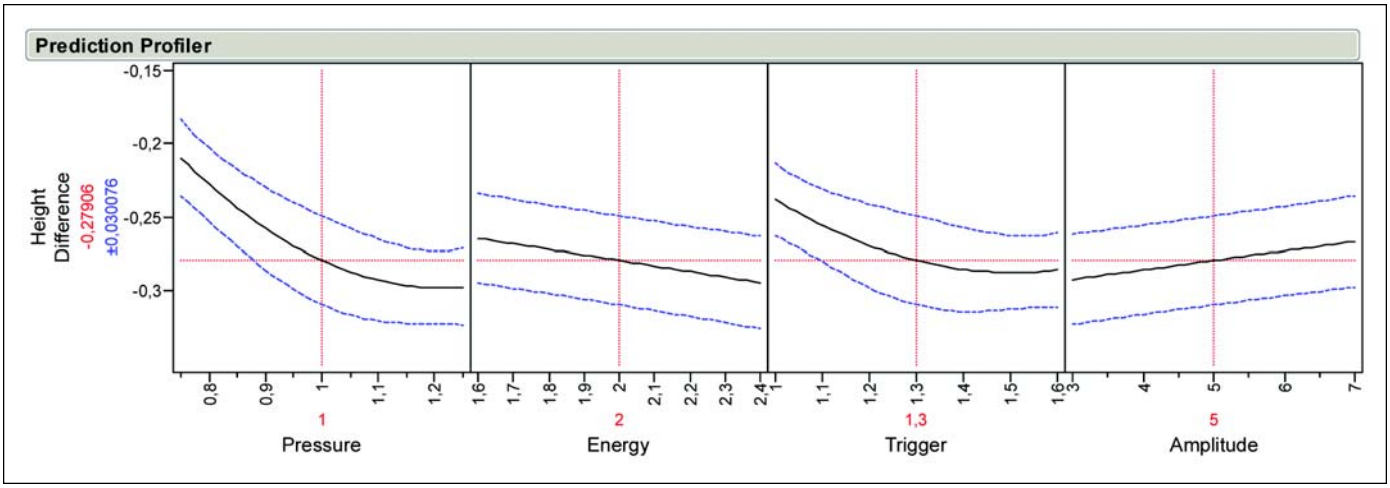


Figure 4. Result of the response surface experiment.

company. Now the users of the processes can perform DoE and SPC with support of their statistics department, instead of the statistics department doing it for them.

Select CTQ Parameters

The customers risk analysis was studied and CTQ attributes were identified. From the risk analysis, the external (seen from the customer) CTQ attributes were the strength of the welding and there was no loose, excess material from the welding, so called flush.

Operationalize the CTQ

Since the inspection had to be made on all welded components, destructive testing of the welding strength was not a possibility. It was necessary to use other characteristic responses to the process that could be measured quickly and non-destructively (i.e., internal CTQ parameters). The height reductions during welding and welding time were chosen. The height reduction is an indicator of the process result. The welding time is an indicator of the process itself. The welding is done with fixed energy, i.e., the welder uses the time needed to deliver the set point energy.

Identify Potential Influence Factors

Together with the process experts, potential influence factors were identified in a process review and the result plotted in an Ishikawa diagram as shown in Figure 3. In the first screening DoE, many factors were investigated. This experiment had the double purpose of finding critical sources of variability and identifying factors for further analysis. This initial study identified both the needs of modification of the height measurement system and a small redesign of the component. Because these needs were identified early in the project (before Factory Acceptance Test), the modifications did not cause any delay in the project.

Establish Relationships

Based on the conclusions from the screening experiment, the most important control variables were investigated in more detail in a Response Surface Experiment. This was done after

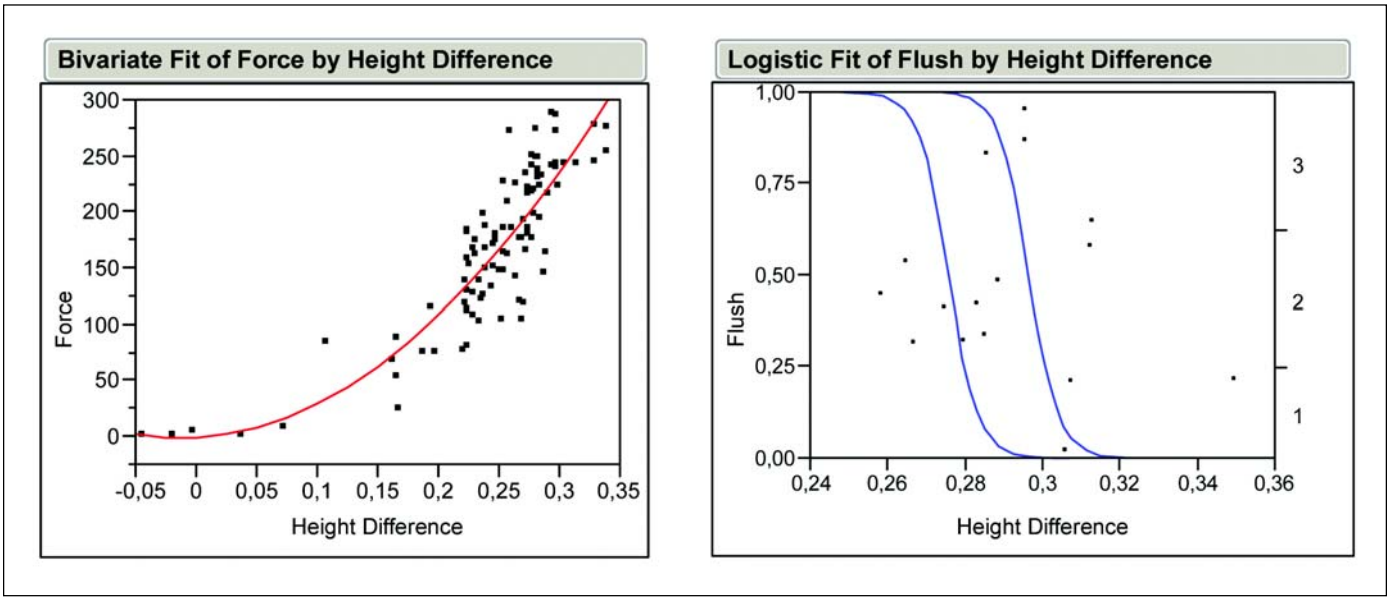


Figure 5. Relation between external CTQ's (separation force left, flush right) and internal CTQ (height difference).

the machine had been moved to the healthcare company. After this study, relationships between both control parameters (Pressure, Energy, Trigger, Amplitude) and internal CTQ (height difference and welding time) as well as between internal and external CTQ (force and flush) were found. Figure 4 shows the result of the response surface experiment, the transfer function between process parameters (Pressure, Energy, Trigger, Amplitude), and process results (height difference). These curves show which parameters are the most critical (i.e., have the largest slope). They also can be used to control the height difference and the welding strength in future production. Since the transfer functions in this case are non-linear, they also can be used to find the settings that will lead to the most constant height difference. Finally, it gives the Design Space for the process, i.e., the process parameter window that will ensure good weldings.

Another advantage of DoE is that it creates samples with a lot of variation in CTQ parameters, which are ideal for correlating internal CTQ (height difference and welding time) to external CTQ (force and flush) as shown in Figure 5. In this way, a specification limit for height difference can be established in a scientific way based on process understanding. It is seen that height difference is a good indicator of both strength and flush. The amount of flush is characterized on a scale from one to three. To the left of the blue curve on the logistic fit is flush grade 1 (low flush) area. To the right of the right blue curve is flush grade 3 (high flush) area. Since the curves are almost vertical, height difference is a good indicator for flush.

Optimize

From the results of the Response Surface Experiment, the optimal setting of the control variables for obtaining the optimal internal CTQ's were found. The optimization was easy to implement since it was only a matter of changing set points for the control variables. With the optimized settings, P_{pk} increased from 0.7 to 2.0.

Control Strategy

To keep the optimized conditions for the external CTQ's (welding strength and no flush) over time it was decided to make statistical control charts on the internal CTQ's (height difference and welding time).

The plot of mean values of height differences versus time is seen in the upper chart on Figure 6. It is easy to read for the operator, who shall monitor if new mean values are in the red zone. If this is the case, actions are needed. Also, the capability and performance index are shown in the table in the upper right corner. Since this process is on target, in statistical control, and follows a normal distribution, there is not much difference between C_p, C_{pk}, $P_{p,}$ and P_{pk}. They are all above 2 equal to Six Sigma quality. Besides being shown on-line at

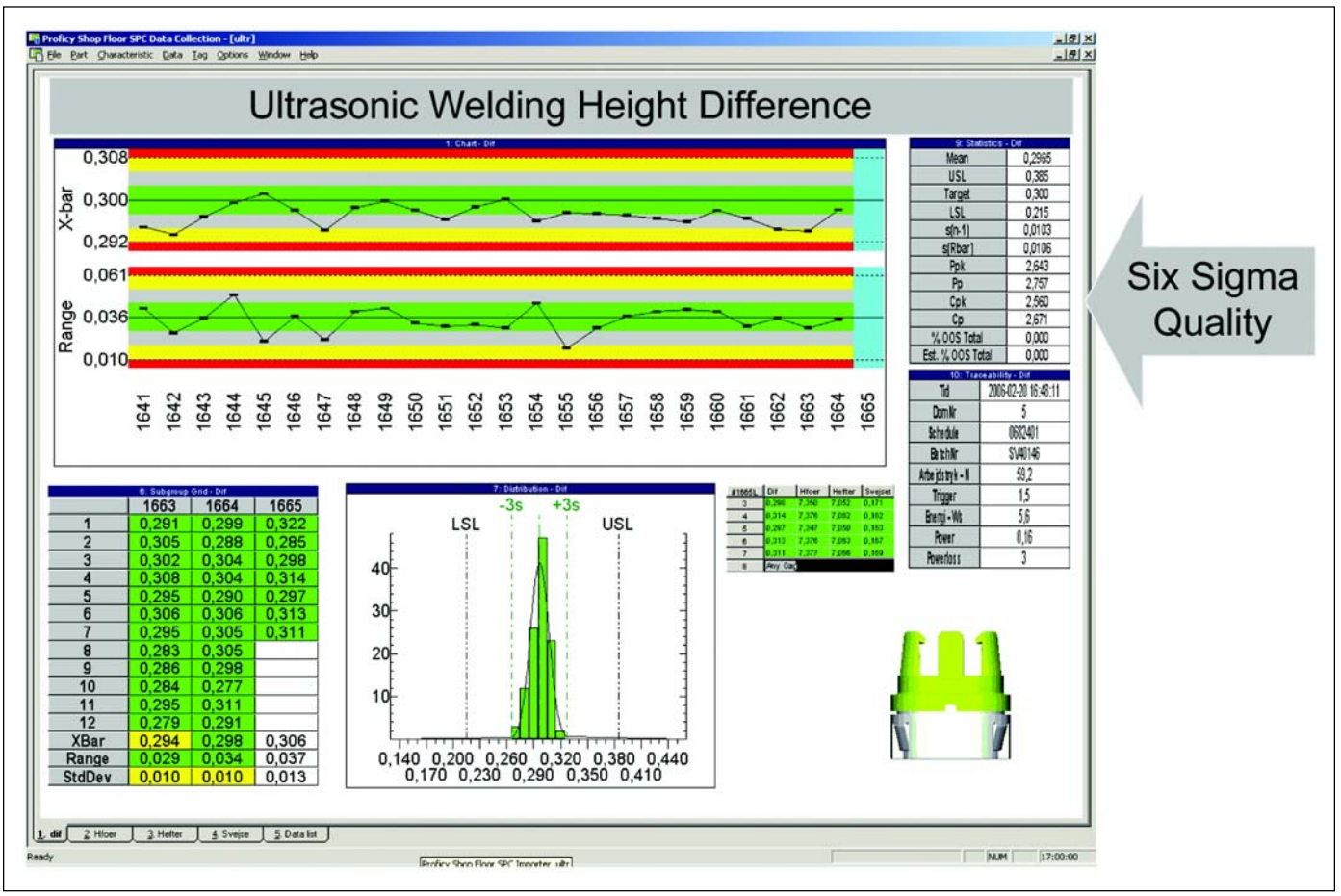


Figure 6. Shopfloor SPC control chart.

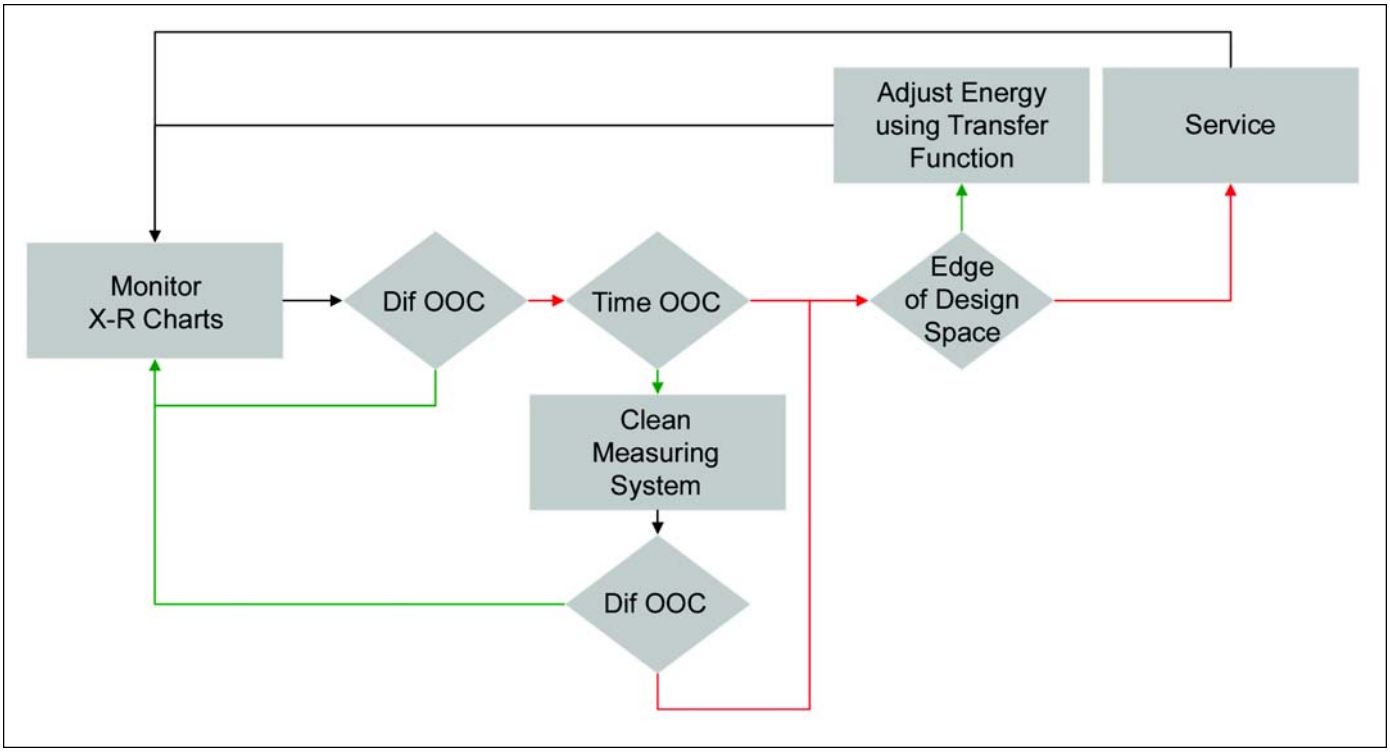


Figure 7. Operator instruction.

the shopfloor in control charts, data also is stored in a database connected to a statistical software package. This allows fast reviewing of historical data, which is being used for continuous improvements and troubleshooting.

When there are new mean values Out Of control (OOC), it is important to have operator instructions for what to do as shown in Figure 7. A typical reason for being out of control is measurement error, not that the process has actually changed. For this reason, a control chart also is made on the ultrasonic welding time. So the first thing the operator does if there are OOC on height differences is to see if there are also OOC on welding time. If this is not the case, the first action will be to clean the height measurement systems because the process indicator (welding time) shows no abnormal behavior. If the cleaning does not help or if both height difference and time are OOC, welding parameters are adjusted or maintenance is performed. The decision to adjust parameters or to do maintenance is dependent on the position within Design Space.

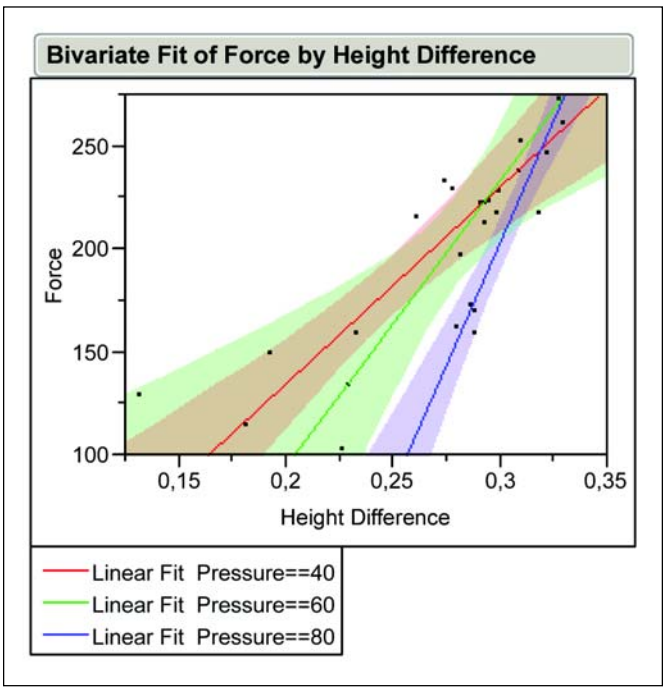


Figure 8. CTQ relations for different pressures.

As can be seen in Figure 4, there are several options for choosing parameters to adjust height differences. Ideally, one should choose only one and fix the others to make it operational on the shopfloor. When choosing the parameter, it can be beneficial to look at how process parameters influence the CTQ relations shown in Figure 5. In Figure 8, it is seen that the lower the pressure, the better the height difference works as a barrier for low forces due to a lower slope on the correlation curve. Therefore, it is not a good solution to use pressure to adjust height difference because it is best to have it at a low value at all times. For this, process energy was chosen to adjust height difference keeping other parameters fixed.

Validate

Due to the process understanding obtained from the DoE experiments, validation efforts were concentrated on validation of the measurement systems and finding the final optimal setting for and correlation between internal and external CTQ's. The latter was done by running a final DoE as a part of Operational Qualification. In this study, it was demonstrated with statistical confidence that the on-line height difference measurements could be used to ensure sufficient

welding strength and low amount of flush. From the DoE, the final mathematical relationship between control variables and height difference also was established (i.e., the final transfer function and Design Space). During Performance Qualification, the validation efforts were concentrated on demonstrating that the process was in statistical control and with sufficient process capability. This was easily documented with data from the SPC database.

Outcome and Benefits

The company obtained a fully operational welding process producing Six Sigma Quality with a P_{pk}>2. The starting point was a P_{pk} of 0.7. This corresponds to a reduction of CoPQ from 25% to 1% of Sales. The process quality is documented during production by in-line measuring of the height difference and welding time for each welding. There is no need for lead time increasing offline QC controls. Due to the SPC system and the established transfer function, the company can now easily keep the process on target from the shopfloor by adjusting the control variables to compensate for changes in raw materials, climate, wear etc. Since the adjustment is based on process understanding, it can be done without change requests.

Conclusion

Implementing PAT tools like DoE and SPC has a high potential to increase quality and lower the costs of pharmaceuticals and medical devices. Alot can be learned by looking at how it was done in other industries. PAT has a lot of similarities with Six Sigma and the pharmaceutical industry should learn from the experience in implementing Six Sigma. Six Sigma cost savings models from variance reduction can be used to quantify PAT benefits. Another important learning from Six Sigma is that the statistical tools like DoE and SPC shall be used by the process users not by statistical experts. The case study shows an implementation example where Six Sigma tools have been used within the pharmaceutical industry to improve quality from a P_{pk} of 0.7 to a P_{pk} higher than 2 and lower Costs of Poor Quality from 25 to 1% of sales.

References

1. http://www.fda.gov/cder/guidance/6419fnl.htm.
2. Abboud, Leila and Scott Hensley, "New Prescription for Drug Makers: Update the Plants," *The Wall Street Journal*, 3 September 2003.
3. http://www-1.ibm.com/services/us/imc/pdf/ge510-4034-metamorphosis-of-manufacturing.pdf.
4. ISO21247 (2005).
5. Watts, D.C., and J.E. Clark, *The Journal of PAT*, Vol. 3, Issue 6, December 2006, pp. 6-8.
6. Department of Defense Test Method Standard, DoD Preferred Methods for Acceptance of Product, Mil-Std-1916, April 1996.
7. ISO21747 (2006).
8. Harry, M.J., Quality Progress, May 1998, pp. 60-64.
9. Clark, T.J., *Success Through Quality,* Quality Press 1999, ISBN 0-87389-441-3, www.successthroughquality. com.
10. DeFeo, Joseph A., *Quality Progress,* Vol. 34, No. 5, May 2001, pp. 29-37.
11. Brindle, A., and Per Vase, "Process Review for PAT – Selecting Cost Efficient PAT Projects," *Pharmaceutical Engineering*, November/December 2006, Vol. 26, No. 6, pp. 70-78.
12. ICH, Q8 Pharmaceutical Development, Glossary, May 2006.

About the Author

Per Vase holds a PhD in materials science and an MSc in experimental physics. He recently joined NNE's Process Analytical Technology team as a data analysis expert, but has more than 10 years of experience from previous employments in various industries. Vase has worked with Six Sigma in New Businesses and has a proven track record of bringing products rapidly from the Research Phase to the Quality Controlled Production Phase by the use of Six Sigma Tools, especially DoE and SPC. Vase has a proven track record in combining compliance efforts with process optimization efforts within the manufacture of medical devices, ensuring both high quality and low costs. He can be contacted by email at: prva@nne.dk.

NNE - Process Consulting, Vandtaarnsvej 108-110, 2860 Soeborg, Denmark.

Exclusive On-Line Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Barrier Vial Technology: A Global Approach to the Aseptic Filling Process

by Diego López-Álvarez, Sergi Roura, and J. A. Garcia

This article describes Barrier Vial Technology (BVT) a technology for the filling of liquids under aseptic conditions.

Introduction

Microbial contamination is a concern and a constant struggle in research laboratories, as well as in sterile medicine production plants. Although the distinguished scientist Alexander Fleming discovered penicillin, one of the most outstanding discoveries of modern medicine, as a consequence of an accidental contamination in a bacteria culture, it is vital to prevent such contaminations in sterile formulas.

In order to minimize the risk of contamination in sterile filling, the industry has implemented more and more rigorous procedures and technologies. As a result, a leading company specialized in the manufacture of plasma derivatives applied its many years of experience to developing an aseptic filling process: *Barrier Vial Technology* (*BVT*)**.** This process has continued to be refined over the last 20 years.

BVT does not simply cover aseptic filling, but every single step of the aseptic process; from the preparation and sterilization of containers and closures to the laser etched identification of vials after dosing. Both liquid and freeze-dried products can be dosed with the BVT sterile filling process. The description of this process in this article refers to a liquid sterile filling plant.

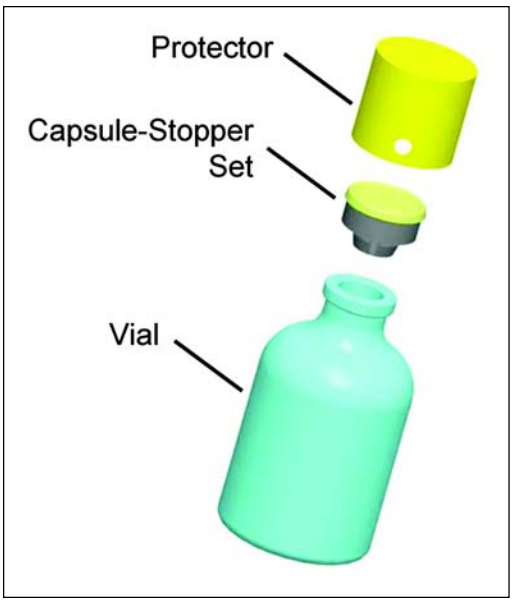


Figure 1. A typical container in the BVT aseptic filling process.

The set of practices and procedures described in this article demonstrate the unique approach used throughout the aseptic process which minimizes the risk of particulate and microbial contamination every step of the way.

The most important safety measures to take against particulate contamination include a high quality clean area and the use of physical barriers to protect sterile containers and stoppers.

Among other relevant features in BVT, the vial is partially closed during handling with physical barriers. The fact that the vial is protected with physical barriers means that contamination risk is extremely minimized. However, the vial allows the steam to enter for a proper sterilization.

Before describing the BVT aseptic filling process in detail, the above mentioned physical barriers are described.

The Container: Description

A typical container handled in the BVT aseptic filling process comprises three elements: a vial, a capsule-stopper set, and a protector - *Figure 1.*

The **vial** is a standard container made of glass or plastic for pharmaceutical or medicinal use.

The **capsule** - *Figure 2*, also is standard, but the **stopper** is specially designed for aseptic processing. The main features of this stopper are:

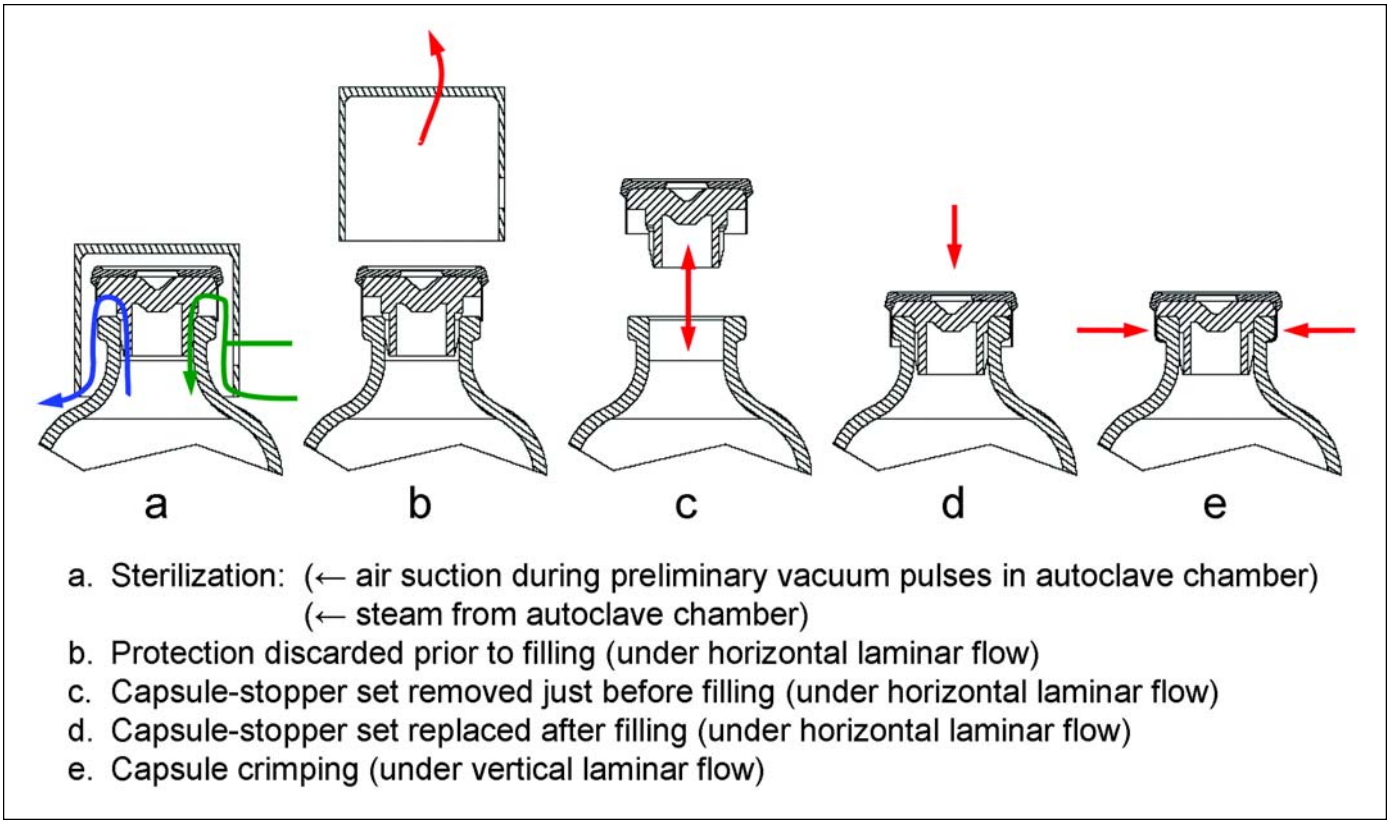


Figure 2. The container in BVT aseptic processing.

- A stepped outside contour allows the stopper to stay in two different stable positions inside the neck of the vial.
  1. partially inserted to allow the container to be sterilized - *Figure 2a*
  2. fully inserted to seal the vial after filling - *Figure 2d*

- A set of grooves in the body of the stopper (similar to the grooves of stoppers for lyophilized products) allows the sterilization steam pass to the inside of the container.

- A flange shape provides a tight fit between the stopper and the capsule.

The **protector** - *Figure 1 and Figure 2a* rests on the vial neck covering the capsule-stopper set. This piece has the following two functions:

1. to create a labyrinth-like path, between the vial and the capsule-stopper set, that prevents particulates from entering into washed and sterilized containers

2. to prevent the capsule-stopper set from being fully inserted due to improper handling before sterilization (only when being handled manually)

The originality of the container is not based on the use of standard vials or redesigned closures, but on the handling of the vial: the capsule-stopper set and the protector are in place on the vial, from the earliest steps of the aseptic processing, creating a physical barrier against microbial contamination.

BVT: Aseptic Process Description

The BVT flow diagram is illustrated in Figure 3.

Container and Closure Preparation

The specially designed, pre-washed, Gamma-radiated, and clean packed stoppers are automatically inserted inside the capsule bodies. The product contact surfaces of the stoppers are rinsed with water for injection and blown with filtered air.

The vials are thoroughly rinsed and blow-cleaned inside and out at different stations to meet pharmaceutical standards in conventional washing machinery.

The capsule-stopper sets are partially inserted into the vials and afterward protectors are simply placed over the vial.

Once this is done, the partial closure creates a labyrinth-like path, which reduces the probability that particulates will be able to enter, but vials can still be sterilized. The container will continue to have a "labyrinth-like seal" until dosing.

Containers are arranged on trays, and the trays are loaded on wheeled racks.

Component Sterilization

Wheeled racks are conveyed into an autoclave where the container (including the capsule-stopper set and protector) are sterilized by moist heat.

The labyrinth-like seal of the container permits the air to be removed with a preliminary stage of vacuum pulses and

then steam to enter and sterilize the vial. Just after the sterilization stage of the autoclave cycle, a drying stage takes place to prevent condensation from forming inside the vials.

The intensive vial washing together with the long sterilization process guarantee the reduction of endotoxins (by at least 3 logs) of the containers as specified in cGMPs.[1]

After the sterilization cycle, the wheeled racks remain under a laminar flow to cool the containers in the aseptic processing area.

Aseptic Filling

Wheeled racks are brought near the filling room. The operator places the containers of each tray onto the infeed rotary table of the filling line.

Dosing takes place in a Grade A (Class 100) environment equipped with a horizontal laminar flow. Inside this area, the protector is discarded.

As soon as the vial reaches the filling point, the capsule-stopper set is removed and the filling nozzle doses the pharmaceutical product. After dosing, the capsule-stopper set is inserted completely into the vial.

Therefore, the amount of time during which the vial remains open within the Grade A environment is reduced to the time required to unstopper the vial, fill and restopper the vial (full insertion).

Unlike conventional filling lines, there is no need for extra machinery to feed stoppers and capsules, because the vial reaches the filling point with the stopper-capsule set already mounted on the vial.

The absence of stopper feeder equipment in the filling area reduces the particulate count and obtains better particle results during monitoring.

A video camera records the whole filling process.

Sealing and Identification

Stoppered vials are conveyed outside the filling room where the capsules are crimped under a laminar flow by means of standard crimping machinery.

The filling and crimping processes take place in different rooms (physical separation and different pressure levels avoiding pressure reversal),[2] so that no particulates generated during the crimping operation will reach the filling area.

After crimping, a laser system marks the batch code, the filling time, and the vial number on the glass vial.

Laser marking is durable and cannot be eliminated without damaging the container. In addition to anti-counterfeiting benefits, laser marking also is helpful for traceability.

The filling process recording and the laser marking is very useful if a quality investigation is performed. Both the filling time, which is etched on every filled vial, and the video recording of the whole filling operation allow complete tracking of the filled units.

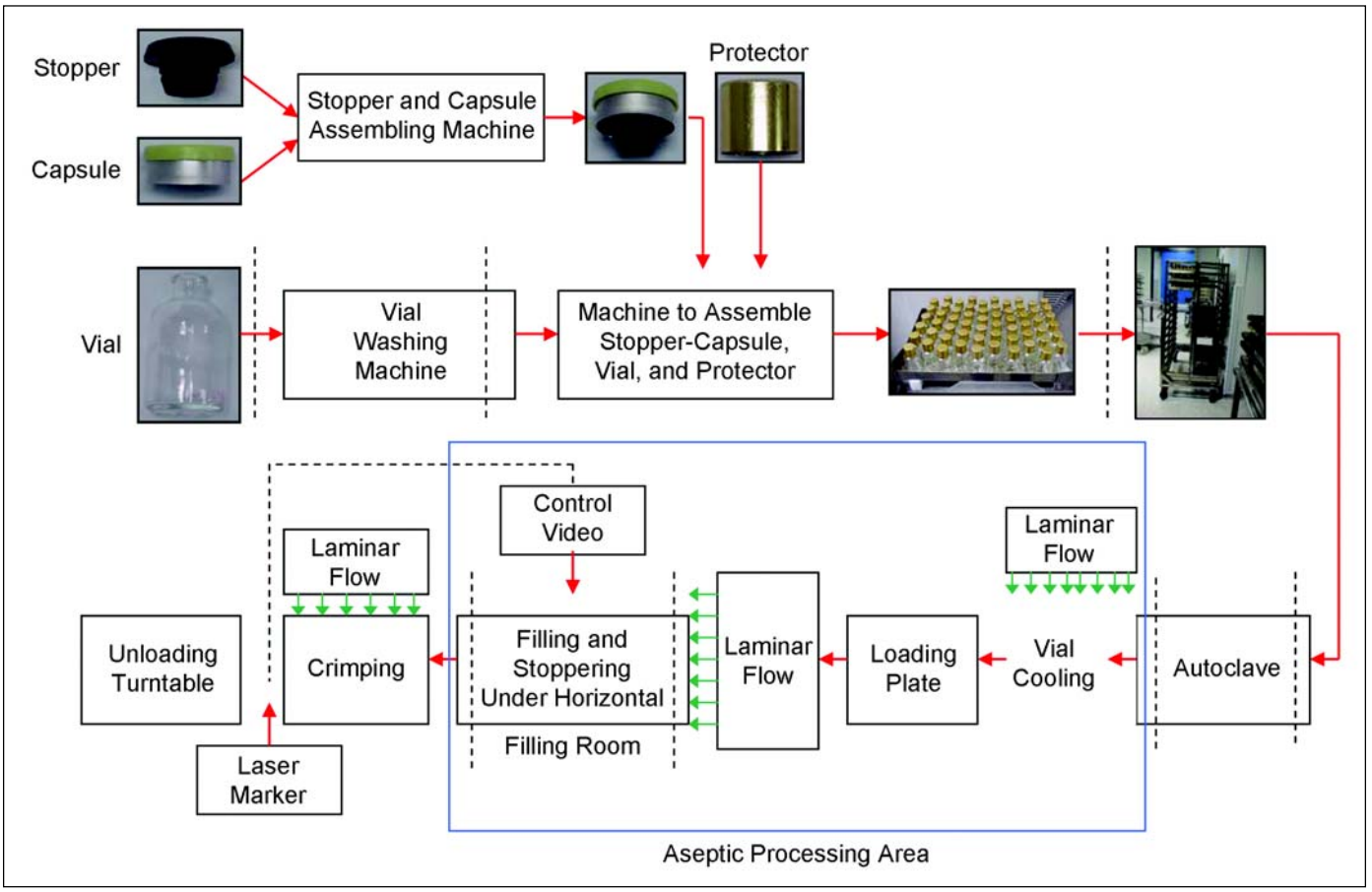


Figure 3. The BVT process

The Filling Suite and the Filling Area

The **filling suite** is comprised of the following four rooms - *Figure 4*:

- the ***vial loading room***
- the ***filling room*** where the **filling area** is located
- the ***vial finishing room***
- the ***service room*** behind the filling room

The operator supplies vials to the filling line from the ***vial loading room***. The control and oversight of the filling line are done from this room. This design features make it possible to minimize the presence of the operator inside the filling room.

The operator's tasks inside the **filling room** are limited to: preparing for the vial filling (set-up the non-viable particulates monitoring system and the sterilized filling equipment which includes tubing, filling nozzles, containers, etc.), troubleshooting, and environmental control for viable particulates.

This equipment is designed to operate in an "at rest" occupancy state (at rest is when the equipment is installed and operating, but with no operating personnel present.")[3a]

Because the container used in the BVT aseptic filling process consists of a pre-assembled stopper (capsule-stopper set - *Figure 1*), the stopper feeding system in conventional filling rooms is eliminated meaning that:

- The operator does not have to enter the filling room to load stoppers into the feeding system.
- There are fewer particles (any feeding device generates particles).

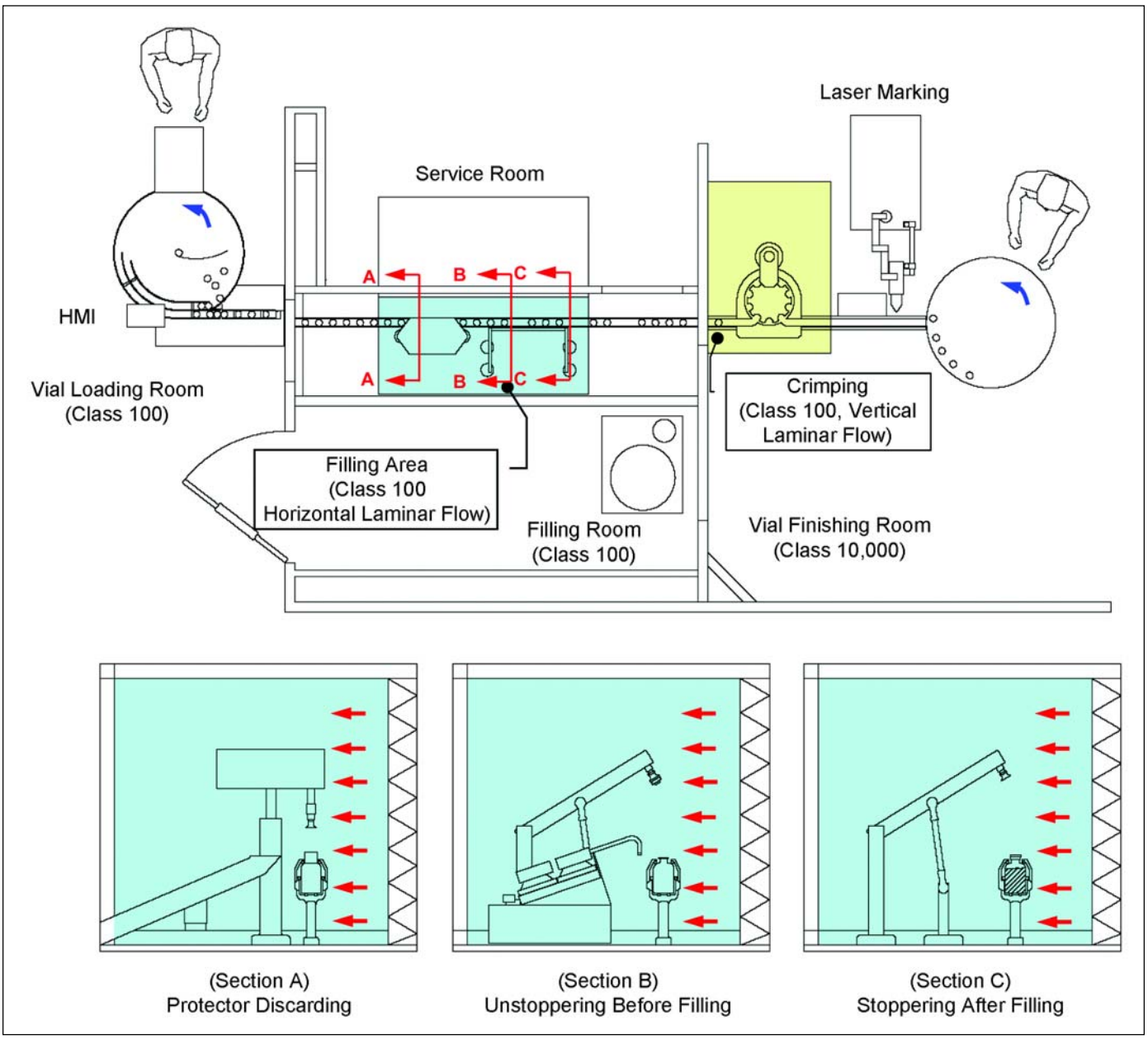


Figure 4. The filling room and the filling area.

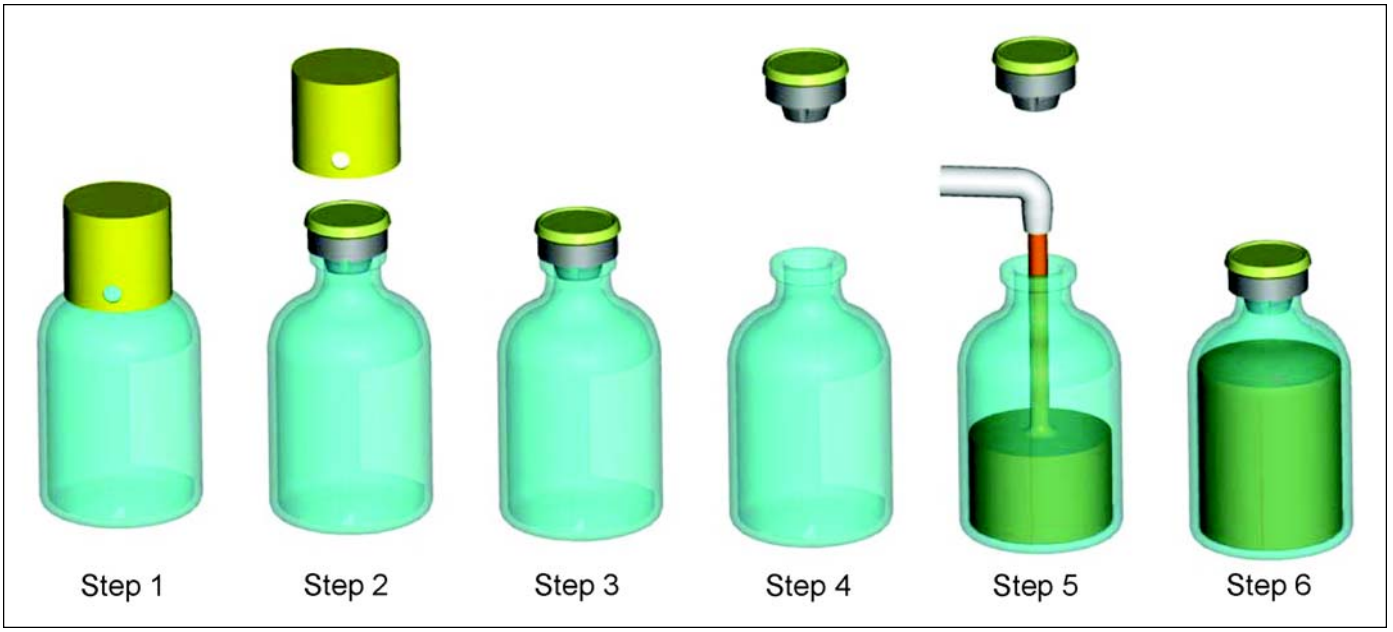


Figure 5. Step-by-step filling process inside the filling area.

- The filling room is smaller.

The filling area (see blue area in Figure 4) is a tiny space protected with a horizontal laminar flow where the following steps take place - *Figure 5*:

- The vial arrives with the protector and the capsule-stopper set already mounted (Step 1).
- The protector is discarded (Step 2).
- The vial moves to the filling position (Step 3).
- The vial is unstoppered (Step 4).
- The nozzle fills the vial (Step 5).
- The vial is fully stoppered (Step 6).

Distinctive features of such an extremely small filling area are:

- **Size:** the height and the length of the filling area has the same dimensions as the HEPA filter of the laminar flow.

- **Horizontal laminar flow:** a horizontal air flow reduces the risk of particulates entering into vials.

- **Proximity of the vial to the HEPA filter (150 mm):** the potential for contamination of air flow that reaches the vial is reduced.

- **Location of equipment within the filling area:** moveable parts are placed downwind of the filling point and are carefully designed to maintain the characteristics of laminar air flow.

- **Vial handling**: a device located outside the filling room pushes the vials into the filling area eliminating belts, chains, and similar conveying systems which are difficult to clean. A sensor system detects the proper positioning of the vial under the filling nozzles.

- **Restricted access:** safety barriers are installed in the filling area to protect the sterility of the process. If the light barrier detects a breach in the filling area, the filling machine automatically stops the process and all the vials are immediately stoppered. If the process is re-started, the machine will run some cycles without filling, reducing the possibility of contamination from intrusions into the filling area.

Once the units are filled and stoppered, the stoppered vials reach the vial discharge room where they are crimped (see yellow area in Figure 4) and laser marked.

Any maintenance is performed from outside the filling room. Because the filling line is integrated into the wall panel, the inside of the machine is accessible for maintenance from the service room in accordance with GMP equipment design recommendations.[3b]

The design of the **filling machine** installed in the filling room is compatible with any filling system: piston pump, diaphragm pump, time pressure system, weight control, disposable filling, peristaltic pump, etc.

The selection of the most suitable system depends on: accuracy (the more expensive the product, the greater the accuracy), volume adjustment (fixed volume versus variable volume depending on product activity), amount of liquid to be filled (small versus big volumes), filling time, batch size, etc.

Validation and Production Experiences

Extensive validation work has been performed to test the protective qualities of physical barriers on sterile containers and stoppers in preventing contamination.

Two studies tested the effectiveness of sterile containers

Figure 6. An example of an existing filling room (human albumin production in progress).

with a physical barrier used in the BVT aseptic filling process - *Figure 1*.

- exposure of sterile containers with a physical barrier to different microbial environments[4]
- an airborne microbial challenge of sterile containers with a physical barrier[5]

The first study consisted of a comparison between sterile open vials and sterile containers with a physical barrier containing sterile culture medium (aseptically filled) when exposed to different environments, specifically grade A, grade B, and "non-filtered air" for a period of seven days.

The results of this study demonstrate that:

- No single sterile container with a physical barrier was found to have microbial contamination after seven days exposure to any environment.

- Every sterile open vial was found to have microbial contamination in the case of non-filtered air, and 1.4% of the sterile open vials were found to have microbial contamination after seven days exposure to grade A and grade B environments.

The second study was an airborne microbial challenge of sterile containers with a physical barrier containing sterile culture medium (aseptically filled). A microbial suspension of bacillus (*Bacillus atrophaeus*) was aerosolized over the containers (inside a sealed chamber) at a final concentration of between 25 and 50 times the maximum microbial level accepted for a grade D area. After 60 minutes of exposure, the containers were fully stoppered, crimped, and incubated for 14 days at 30 to 35°C.

The results of this study show that in both concentration cases, not a single container with a physical barrier had microbial contamination after having been exposed to environments between 25 and 50 times the limit allowed in a grade D area.

The results of these studies demonstrate that the "labyrinth seal" created by the vial and the physical barrier increases the safety against microbes of aseptically filled containers.

If "bacteria-carrying particles in room air are large and that gravitational settling is the most important way they are deposited,"[6] it can be asserted that containers with a physical barrier contribute to minimizing the risk of contamination of the vials, because potential microbe-carrying particulates should not be able to overcome the "labyrinth seal" against gravity.

Taking into account that personnel is the primary source of bacterial contamination in an aseptic cleanroom, the two key factors that increase the confidence of sterility of filled units are the "at rest" occupancy state of the filling room and the physical barrier of the container.

The BVT aseptic filling process is used for the manufacture of injectable products derived from human plasma approved by the FDA and European authorities.

BVT has been developed over the course of the last 20 years, adding improvements and integrating the latest technology in areas such as filling techniques, microbial control, or machine automation.

Media fill simulations have been done extensively following BVT procedures and practices at existing production facilities. More than 350,000 vials have been filled with media since 2002 using the Barrier Vial Technology and no revalidation has been necessary for any batch.

Advantages of BVT

BVT offers four advantages over the conventional aseptic filling process:

1. Particulates and Microbial Safety

- Vials are kept closed, though not hermetically, thanks to the "labyrinth seal" existing between washing and filling. This means that the time the sterilized unit is exposed to the environment is minimized.
- Capsule and stopper feeding equipment (sources of particles) is not needed within the filling room.
- Horizontal laminar flow reduces potential risk of particulate entry into the vial.
- Vials stay very near the laminar flow during the filling.
- The equipment inside the filling area is placed downwind of the filling point, and was carefully designed to avoid air disturbances.
- There is no need for the operator to work inside the filling room, limiting his/her intervention to critical areas (only for troubleshooting and environmental control).
- Maintenance is performed from outside the filling room thanks to the design of the filling line embedded in the wall.

2. Environmental Control

- The small filling area makes it easier to monitor both viable and non-viable particulates, and it is easier to guarantee its integrity.

3. Traceability of Filling Operations

- Video recording together with the laser marking means that the dosing process can be tracked.

4. Cost and Size of the Installation

- Less machine intensive: depyrogenation tunnel versus autoclave (the autoclave is needed anyway in the conventional approach).
- The overall size of the facility required for BVT is much smaller than conventional filling and easier to maintain and validate than conventional processes.

Disadvantages of BVT

The use of an autoclave for the sterilization/depyrogenation of containers (plus a previous intensive washing of the vial) limits the BVT aseptic process to batch production (as opposed to continuous production).

The autoclave must be designed according to the expected maximum batch size.

It should be observed that in order to minimize the time during which the vial is open and exposed to the environment, the three operations: unstoppering – filling – stoppering must be performed sequentially (see sections A-A, B-B, and C-C in Figure 4). This means that unstoppering the vial for filling and stoppering the vial for sealing increase the cycle time. Therefore, the throughput of the machinery designed for BVT aseptic filling is slower than conventional filling lines.

These two disadvantages make the BVT aseptic process suitable for small/medium batch sizes (from 20 vials up to 11,000 vials).

Further Developments

Experimental studies and tests are being performed to integrate the protector element in the capsule.

As described in a previous section, the containers used in the BVT aseptic filling process are made up of three elements: a protector, capsule-stopper set, and vial. It also was mentioned that the capsule was standard and that the vial was crimped by means of standard machinery.

A plastic capsule which clips to the vial has been designed. The special design of this plastic capsule is long enough to play the role of the protector performing the "labyrinth seal."

The three main advantages of this protector-capsule are:

- reduction in the number of components being handled along the BVT aseptic process
- substitution of the crimping machine with a simple press to clip the capsule-stopper set in the vial and consequently eliminate the particles generated during crimping
- complete sealing of vial in front of a Class 100 horizontal laminar flow immediately after filling

The BVT aseptic filling process also is applicable to the sterile filling of freeze dried products. After a vial is filled with a freeze-dried product, the protector-capsule, which includes the stopper, partially stoppers the vial allowing the lyophilization process to occur. The shelves of the freeze dryer then clip the protector-capsule, securely closing the vials. Therefore, the use of the protector-capsule for freeze dried products eliminates the need for crimping found in a conventional manufacturing process.

These most recent advantages meet the requirements stated in the recent proposed revision (approval pending) to Annex 1 of EC Guide to Good Manufacturing Practices: "The container closure system for aseptically filled vials is not fully integral until the aluminum cap has been crimped into place. Vials should be maintained in a Grade A environment until the cap has been crimped"[7] (clause 93).

There is a BVT specifically adapted for the aseptic filling process in extremely small batch sizes of personalized medicines. In these cases, the drug product losses are minimized thanks to the full drainability of the filling system.

Furthermore, the system can be mounted and installed in a modular cleanroom delivered and pre-validated prior to the factory acceptance test.

Conclusion

Barrier Vial Technology (BVT) is an aseptic processing approach for high value-added pharmaceutical products, such as biotech medicines, plasma derivatives, and others which are not stable enough to undergo final product sterilization by heat. BVT is applicable both to liquid and freeze-dried products.

Although some similarities with conventional aseptic processing exist (vial washing process, integration of any filling systems - time pressure system, weight control, peristaltic pump, etc.), BVT increases microbial safety of aseptically prepared products and maximizes the exclusion of particulates from all phases of aseptic processing.

BVT offers advantages such as particulates and microbial safety, environmental control, traceability, anti-counterfeiting, and lower facility costs when compared to conventional procedures.

BVT has been employed for the last 20 years in a plasma derivatives factory approved by the FDA and European authorities for the production of medicines.

References

1. U.S. Department of Health and Human Services (Food and Drug Administration), "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice," p. 17, September 2004.
2. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 3 - Sterile Manufacturing Facilities,* International Society for Pharmaceutical Engineering (ISPE), First Edition, January 1999, p. 23, www.ispe.org.

3a. 3b. Ad Hoc GMP Inspections Services Group (European Commission), "Manufacture of Sterile Medicinal Products - Medicinal Products for Human and Veterinary Use," EU Guidelines to Good Manufacturing Practice, May 2003, Vol. 4, Annex 1, clause 3, clause 33.

4. Instituto Grifols, "Evaluation of the Contamination of Sterile Vials to Different Exposure Conditions," IG_ITEC-

000244_ING, internal report, 2006.
5. Instituto Grifols, "Demonstrating the Effectiveness of Physical Barriers in Sterility Assurance of Vials Subjected to Airborne Microbial Challenge Test," IG_ITEC-000244_ING, internal report, 2006.
6. Whyte, W. "Sterility Assurance and Models for the Assessing Airborne Bacterial, Contamination White," *Journal of Parenteral Science and Technology,* Vol. 40, No. 5, September – October 1986, pp. 1996.
7. European Medicines Agency – Inspections, "GMP Annex 1: Proposals for amendment to the environmental classification table for particles and associated text, amendment to section 42 concerning acceptance criteria for media simulations, amendment to section 52 concerning bio-burden monitoring, and additional guidance in section 88 on the sealing of vials," September 2005, clause 93, pp. 4.

Acknowledgements

The authors of this article would like to thank Dr. Victor Grifols, inventor of the Barrier Vial Technology, for his comments and suggestions during the writing of this article, as well as Instituto Grifols, for the information provided on the validation of this technology.

About the Authors

Diego López-Álvarez, EMBA from ESADE Business School, MSc, industrial engineer, is responsible for the Applied Engineering Department at Grifols Engineering and is involved in the development, design, and innovation of tailor-made machinery for the pharmaceutical companies of Grifols Holding and third-parties. He has led, promoted, coordinated, and installed a number of aseptic filling processing lines in European and American facilities, applying Barrier Vial Technology (BVT) for high added value products (liquids and freeze-dried): therapeutic proteins from human plasma (coagulation factors, albumin, etc.). Among his last assignments, he managed and planned the design, construction, and start up of several fully automatic lines for the filling of terminal sterile products (parenteral solutions), blood typing reagent cards (gel products), as well as machinery for the molding of plastic bags for medical use. López has contributed to the improvement of a number of pharmaceutical manufacturing processes such as vacuum inspection in sealed glass containers and aseptic filling. In addition, he has done consultancy in the field of advanced machinery and laser marking for important companies within the pharmaceutical industry. He can be contacted by e-mail at diego.lopez@grifols.com.

Sergi Roura Adell, Industrial Engineer, is Managing Director of Grifols Engineering and holds a PPD from IESE Business School. He is currently running an engineering company specialized in biotech process and machinery development. Roura is responsible for the engineering technology of the Grifols Holding. His areas of expertise include finished pharmaceutical manufacturing, biotech processes, and clean process utilities (Pure Steam, Water-For-Injection, USP Purified Water, CIP, sterile filling, etc). Roura has been involved in the design and construction of manufacturing plants worldwide, mainly for biotech sterile products. Prior to that, Roura worked as project engineer in ATC in Los Angeles. He is a member of ISPE since 1994 and is the President of the ISPE Spanish Steering Committee. He can be contacted by e-mail at sergi.roura@grifols.com.

Grifols Engineering, 2, Can Guasch, 08150 Parets del Vallès, Spain.

Juan Antonio Garcia is Vice President of Manufacturing of Grifols Biologicals, Inc. He holds a degree in pharmacy and an MBA in the Escuela de Administracion de Empresas (Barcelona). As Head of the Validation Department of Instituto Grifols for more than 10 years, he acquired a deep knowledge of sterile filling processes, sterilization, cleaning, and control of cleanrooms, virus inactivation processes, as well as pharmaceutical process machinery. Since January 2004, Garcia has held the role of Vice President of Production in Grifols Biologicals, leading the manufacturing of the plasma derivatives plant in Los Angeles. He can be contacted by e-mail at juanantonio.garcia@grifols.com

Grifols Biologicals, Inc., 5555 Valley Blvd., Los Angeles, California 90032.

Exclusive On-Line Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Pharmaceutical Manufacturing: Linking Vision and Decision-Making to Achieve a Roadmap Toward cGMPs for the 21st Century

This article presents the changing manufacturing environment and how companies can develop an infrastructure to continue to meet their strategic objectives.

by Beatrijs Van Liedekerke and Ingrid Maes

Introduction

Despite the innovatory and advanced science nature of many of its products, the pharmaceutical industry has been more used to incremental change in manufacturing rather than quantum leap advances. Now, however, there is the prospect of more rapid change in the industry. Changes in the regulatory stance and compelling business reasons are prompting companies to consider 'big leap' rather than 'small step' changes. But many companies remain wary of drastic change. How can companies judge how best to prepare for the future manufacturing strategy and infrastructure? How fast and how far should they move? Many companies are seeking to implement manufacturing change, but are doing so in sub-optimal ways that do not maximize benefit for the company. This is because, often, changes in manufacturing practice and infrastructure are not being informed by a clear manufacturing vision. Such a vision must address the regulatory, market, scientific, and technological forces that will shape pharmaceutical manufacturing in the future. Changes in regulation and technology are already influencing how existing products are tested. Looking ahead, regulatory, scientific, and technological developments have the potential to produce significant change in the interaction of manufacturing and the market. This article considers this changing context and looks at how companies can develop a manufacturing vision. It outlines four possible manufacturing scenarios that companies may find themselves considering. The IT/manufacturing infrastructure that will be important for each scenario is presented.

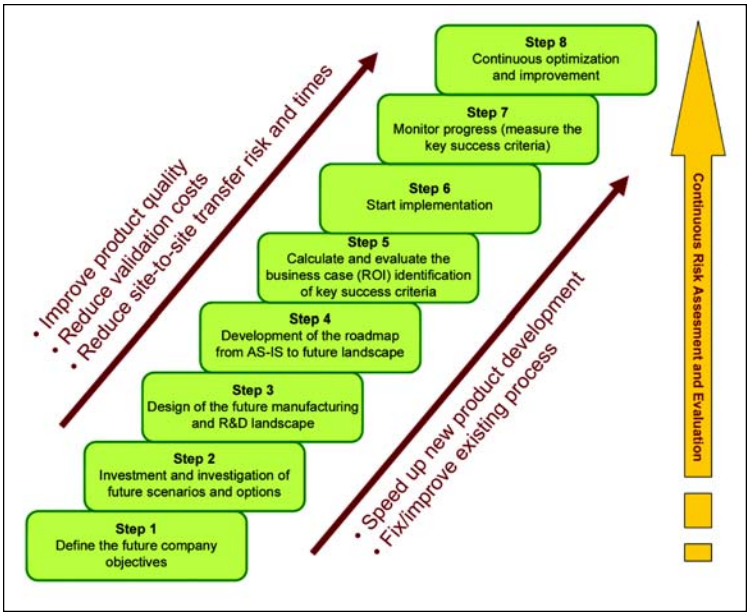


Figure 1. Moving toward the manufacturing vision.

The Changing Manufacturing Context

The pharmaceutical manufacturing sector has been inherently conservative in its approach to manufacturing change. Regulation is a key driver for change. Historically, though, the regulatory framework, with its reliance on batch inspection, has de-

terred manufacturing innovation. Regulation has driven change, but in an 'after the event' fashion with compliance reliant on enforcement and inspection. Now, recent initiatives of the US Food and Drug Administration (FDA) herald an era where regulation can act as a more dynamic driver of change with both quality and regulatory compliance 'designed in' to the manufacturing process. The FDA's PAT framework and its cGMPs for the 21st Century initiative provide significant opportunities for improvement and innovation in pharmaceutical manufacturing. The FDA talks about a 'desired state' of manufacturing with:

- product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- an ability to affect continuous improvement and continuous "real time" assurance of quality[1]

The final report of the FDA's cGMPs for the 21st Century Initiative[2] highlights the choices that pharmaceutical companies face:

> "At the end of the cGMP initiative, the pharmaceutical community has arrived at a cross-road; one path goes toward the desired state and the other maintains the current state. The path toward the desired state is unfamiliar to many, while the current state provides the comfort of predictability. The Agency hopes the pharmaceutical community will choose to move toward the desired state."

This new regulatory approach presents companies with the possibility of new manufacturing visions. It also comes at a time when the risk reward context for pharmaceutical manufacturing is changing. Companies are becoming more exposed to powerful wider market forces. The pharmaceutical industry is at a key turning point in many respects. Historical ways of delivering value will not be sustainable on their own in the future. All the key planks of value are in transformation – drug development pipelines are drying out, pricing is under pressure, and generic competition is more intense. Cost containment is the name of the game both for the government customer bodies that play a lead role in the pharmaceutical market around the world and the private insurance customers in mar-

Case Study 1: Manufacturing Vision Development

Background

A pharmaceutical company has a product that will soon run out of patent and generic manufacturers are becoming strong competitors. Reducing manufacturing costs has been defined by this pharmaceutical company as a key business objective.

A Typical Response

The company decides to appoint a team of experts whose task is to review manufacturing and propose optimization proposals. After a couple of months, this team presents the cost reduction initiatives to their management. A list of suggestions have been made, such as better planning to remove Work In Progress (WIP) and to lower inventory; optimization of manufacturing yields and costs by enlarging the batch size (higher filling levels in manufacturing equipment); in-line inspection instead of manual inspection; and installation of process analyzers to detect batch end-points, for example for drying and blending. The team shows that these measures will deliver a reduction in manufacturing costs.

A 'Manufacturing Vision' Response

Another company takes a different approach. Instead of appointing a team to look for optimizations and improvements, it first organizes a high level meeting with representatives from a range of departments - R&D, manufacturing, sales and marketing, regulatory affairs. The aim of the meeting is to investigate what will be needed in five to 10 years time, taking account of business challenges, technological options, and regulatory opportunities.

The group has already looked at their current product portfolio and future portfolio, based on their pipeline. It has investigated the consequences of this new portfolio on the current manufacturing infrastructure. It has considered what the future manufacturing landscape will look like to be able to cope, not just with the new product portfolio, but also with the future market and environmental requirements, business model requirements, regulatory changes, etc. A scenario planning exercise has supported the exploration of possibilities and future scenarios. This study results in the identification of a manufacturing vision, which describes the future required manufacturing landscape that will best fit with the most likely scenarios.

This vision makes it easier to identify the gaps between the current "as is" manufacturing situation and the future "to be" one. It also helps to indicate the improvements and changes that the company can already start to implement. A roadmap linking the "as is" and the future "to be" situation enables the company to focus on the improvement and optimization projects that help it move to the future situation. The company can avoid investments which, taken in isolation, might have a sufficient Return On Investment (ROI) to implement, but when looked at in a fuller context, would not achieve a more sustainable advancement for the company. This broader perspective enables the company to move forward in the knowledge that it is not just investing in little islands of optimizations, but is linking them to a wider and bigger quantum leap forward.

kets such as the US. Double-digit sales and income growth has come to an end under pressure from patent expirations, generic competition, and Over The Counter (OTC) switches.

Alongside these trends, we are not so far from a future where it will be possible to develop drugs that are tailored to the individual genetic and proteomic profile of the patient, making the therapy more effective and having less side-effects by optimizing dosage and drug composition for each patient. An investigation by the national academy of science of the UK concluded: "personalized medicines; tailoring drug treatments to a person's genetic profile, also known as pharmacogenetics, have a promising future,"[3] predicting that "over the next 10 to 20 years, we expect to see several pharmacogenetic products enter mainstream healthcare."[4] The report pointed out that "industry will continue to favor drug candidates that avoid the effect of genetic variation, but where that is not possible, the development of drugs with an associated diagnostic test is expected to become routine in the next 10 to 20 years."[5] In part, mainstream pharmaceutical M&A companies have reflected this future with repeated acquisitions of biotechnology companies. These moves have been designed to boost drug pipeline portfolios in the short to medium term and build capacity for a more genetically-driven industry of the future in the medium to long term.

Such a future is very relevant to a company's manufacturing vision. As a consequence, drugs will need to be manufactured or produced in smaller batches that are formulated on request to match the profile of certain segments of patients or even a single patient. There will be fewer big blockbuster drugs and more personalized medicines. To accommodate these changing production needs, new flexible regulatory approaches and batch control strategies have to be developed. Moreover, since the treatment is formulated on request and is intended for a patient who may urgently need the medication, product development and manufacturing lead time and release times will have to be drastically reduced.

Developing a Manufacturing Vision

Therefore, pharmaceutical manufacturers face a complex and in some respects, contradictory set of demands. On the one hand, they have the opportunity to make significant investments in automation and process technology, but on the other hand, they face cost pressures, meaning that such investments must deliver the maximum benefit. They face a future drug market that may be more personalized, posing key dilemmas for whether the manufacturing plant development should be large scale or small scale.

Mergers and acquisition activity has made it easier for some companies to close or modify existing outdated plants. In our practical experience, we see companies starting a lot of investment projects both as part of post acquisition activity and elsewhere. They are called various names, such as improvement projects or cost containment projects, but they have in common the aim of manufacturing modernization. However, they are rarely informed by a real look at the bigger picture of where the company wants its manufacturing to be in five to 10 years time (see Case Study 1). Classically, when companies consider investment in Process Analytical Technology (PAT) for example, they often see it as replacing one form of testing with another form of testing without considering its full potential. No wonder Dr. Ajaz S. Hussain, who at the time of being quoted was Deputy Director at the Office of Pharmaceutical Science CDER at the FDA, was prompted to remind companies: "you've got to remember that PAT is not about just throwing in-line sensors at a production line. It is more about understanding the sources of product variability during production and controlling your processes in a flexible way to allow you always to produce a quality product."[6]

Investment tends to be on a limited scale and fragmented, focusing perhaps on one production unit or process, but not making connections across the manufacturing software and infrastructure which, often, remains standing alone or only present on isolated production units. This often results in sub-optimizations instead of an overall optimization. In the future, the requirement will be for all the supporting software and different applications to be interconnected. As Graham Cooke, Director Technology and External Supply EMEA of Wyeth, has emphasized, companies need to avoid developing isolated islands of innovation: "'Islands' of PAT (need) to be tied together as part of an overall strategy. Feed back and feed forward controls. (Companies need to) develop the 'integrated plan' first and then create focus and dive deep into individual unit operations before extending to other unit operations."[7] In addition, whether it is PAT or other innovation, the infrastructure will need to be of high quality and reliability because the recourse to running the production manually will not be an option.

How can companies judge how best to reshape their manufacturing strategy and infrastructure? In the context of PAT, Cooke emphasises the need for 'wider company' multi-disciplinary thinking: "…a number of success factors have been identified for implementation of PAT. These include the need for multi-disciplinary project teams, a clearly defined implementation process, and a strong business rationale."[8] Companies need to address the culture change implications of investments such as PAT which include breaking down silos within organizations and also rethinking job roles. Far-sighted companies seeking to capture the full competitive advantage potential of PAT will, for instance, be looking at the links outside of manufacturing into the consumer-facing functions of product development and marketing. Skill-set requirements will change significantly. Enterprise-wide data management, retrieval, and querying will be vital. Pharmaceutical scientific skills will need to extend into understanding the supportive database structure and be capable of managing knowledge retrieval systems in an efficient, usable, and timely manner.

In our view, the starting point has to be the manufacturing vision and all parts of the business need to be in-

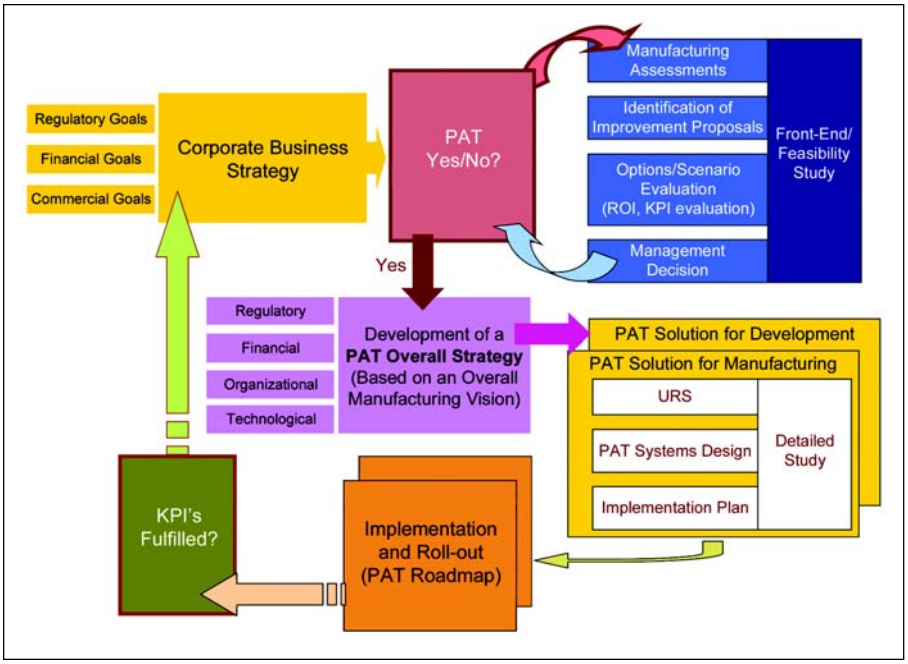


Figure 2. The pharmaceutical manufacturing change context.

volved in looking ahead on a 10 to 15 year time frame. The following case illustration highlights the importance of framing decisions in such a context and contrasts that with the typical approaches that we, as authors, see many pharmaceutical companies taking.

The approach outlined in Case Study 1 allows companies to prioritize specific problems within the context of long-term change. The range of specific concerns could include a need to fix or improve existing processes, speed up new product development, reduce site to site transfer risk and times, reduce validation costs, or improve quality reliability. Most companies are likely to want to realize a blend of these benefits. Their immediate priorities will be determined by the current state of play of their manufacturing and its fit with their regulatory compliance, market and business goals. Most importantly, though, they need to combine this review of current wider concerns with the type of longer-term wider scenario planning outlined in the case illustration above. Figure 1 outlines the steps companies might take to put this process into practice.

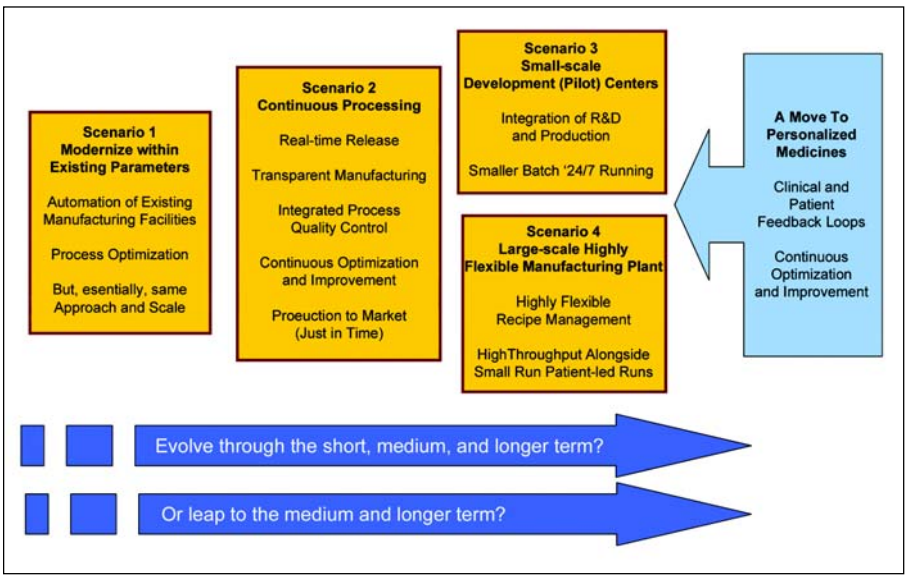


Figure 3. Four change scenarios.

Figure 2 provides an overview of the type of overall decision-making process that a company needs to undertake. The current manufacturing infrastructure has to be assessed in the light of the future manufacturing vision (in line with the global company's objectives). What are the current bottlenecks and what are the improvement possibilities? The resulting list of improvement proposals have to be evaluated to judge just what they bring to the company and whether they help achieve the manufacturing vision and its objectives. Depending on which market the company is in, the regulatory constraints need to be superimposed in order to make sure no surprises are encountered. Even for those countries that are actively driving changes (such as the FDA in the US), it is important to involve the regulators early on in the process.

Four Change Scenarios

The outcome of this type of process will be a view about what type of manufacturing strategy and plant the company needs in a more medium to long term timeframe, say five to 10 years time. The answer may be different from plant to plant and many companies are likely to need to plan for a mix of scenarios. For example, a company may choose to implement relatively modest improvement investment in a plant that is manufacturing a product that is nearing the end of its patent period (scenario one in Figure 3). Elsewhere it may choose to plan for a rapid and full scale move to PAT enabling full realization of the FDA's vision of real time product control and release, based on continuous manufacturing operations (scenario 2 in Figure 3).

Companies also will be mindful that a possible trend toward more personalized medicines will increase manufacturing complexity, and in turn, pose challenges for Manufacturing Execution Systems (MES) and quality systems. A larger variety of products and variation of the same products will require greater flexibility of production as well as closer integration along the whole pharmaceutical chain - R&D,

manufacturing, sales, and the end customer.

Scenarios three and four in Figure 3 highlight how companies will face a choice between big plant with flexible recipe production versus small-scale development (pilot) plants which also will be production facilities with dedicated lines. For both models of production, industrial IT systems will play a strategic role, requiring tremendous flexibility, in the first model, to support the flexibility of production that will be necessary, and in the second smaller scale model, to link production with continuous development and learning from clinical trials. The regulatory stance will be a key factor in this mix and at present, regulators are investigating how to support this evolution with the appropriate regulations and guidelines.[9]

A key influence will be the demand side and we are likely to see a mix of large scale, very high throughput facilities handling generic production, and micro-process centers concentrating on higher end personalized medicines. Therefore, pharmaceutical companies need to investigate the investment in planning for a potentially very different manufacturing future as well as responding to pressures on their current manufacturing set-up.

Choosing Between Scenarios – Evolution or Drastic Change?

A critical issue for companies contemplating scenarios such as outlined in Figure 3 will, of course, be how to make choices between them. The identification of the right evaluation criteria (Key Performance Indicators (KPIs) for improvement) is crucial for evaluating the options and for monitoring progress and achievement of the objectives. Each company's situation will be different and judgements on the focus and pace of change will vary according to the ROI analysis of the different options open to them. For example, some companies may consider that certain plants or processes do not merit investment, others will only need minor investments and others require drastic

Case Study 2: Status Quo vs. Automation vs. Full PAT Implementation in a Vaccine Plant

Background

A vaccine plant was seeking to achieve cost savings through modernization of manufacturing infrastructure. Interviews with different stakeholders and analysis of manufacturing data led to:

- the identification of areas for cost savings through the assessment of possible improvement scenarios
- an outline of operational and financial benefits for these various scenarios
- assessment of the impact of different scenarios on the following KPIs:
  - labor (people)
  - manufacturing throughput time
  - quality
  - waste
  - inventory levels

Improvement Scenarios

Three improvement scenarios were identified. Each of these scenarios describe the various steps toward optimal PAT-enabled manufacturing, delivering the maximum benefits in terms of cost savings.

The scenarios are built up in such a way that maximum benefits are realized with minimal investments. They start with the quick wins followed by a sequence of medium to longer term improvement investments. Each improvement investment goes hand in hand with benefits which are displayed as an effect on the Key Performance Indicators (KPIs).

- Some of the scenarios can be executed in parallel; however, when activities are carried out in parallel, the necessary skilled resources need to be available in order to deal with the complexity and the project management.
- A timeline was developed illustrating how much time it takes to implement the improvements as well as the resources and skill set needed for each of the improvement projects. The time to get regulatory approval should be superimposed on the outlined project execution time lines.
- In parallel with the timeline, the sequence of investments needed to realize improvements was established.

Results

The result was a calculation of the optimal scenario (in this case, scenario 3) and its impact on the KPIs:

- Labor: 1/4 of operations people could be re-allocated and 1/3 of the QA/QC people could be freed up for other work.
- Manufacturing throughput time: throughput time decreased with 1/3 freeing up capacity and allowing extra production with the same headcount.
- Quality: 13% of the cost of QA and QC are eliminated because of improvement in right first time.
- Waste reduction: 3.5%
- Inventory: inventory could be reduced by 1/3 (representing about US $14.3 million in this case).

Observations

In terms of PAT implementation, maximum benefits were achieved with a broad PAT definition. This means looking at the full opportunities offered by PAT, as outlined in the FDA PAT Guidance (e.g., real-time product release, manufacturing performance improvement, quality consistency improvement, and regulatory flexibility). This was preferable to a "limited PAT" approach based only on the implementation of an on-line sensor. We found that the feasibility of a broad PAT enabled manufacturing process could be demonstrated with much more certainty.

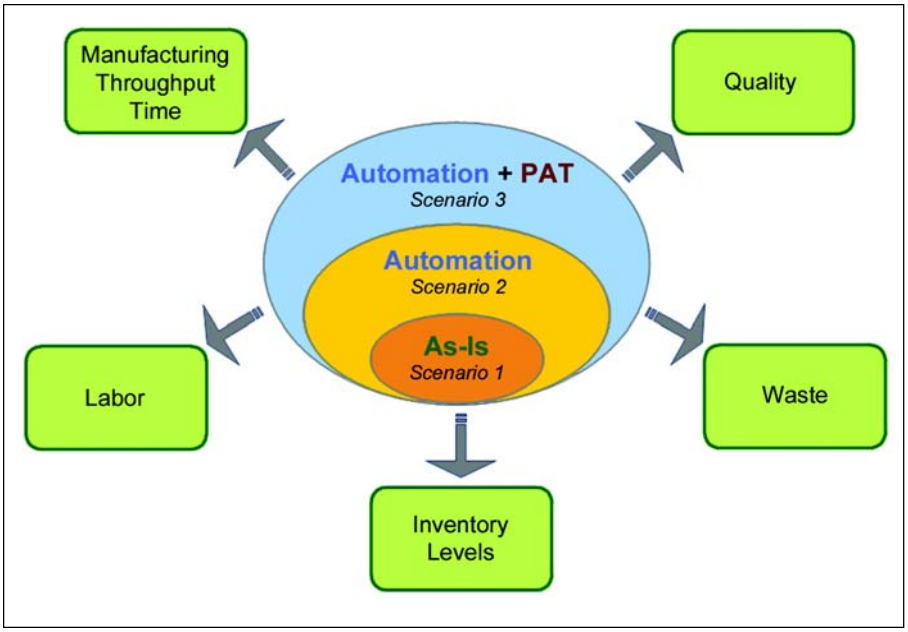


Figure 4. Impact of scenario implementation on various KPIs.

change.

Even in the case of drastic change, it is the authors' experience in many real-life cases that a change, which at first sight may appear quite drastic and associated with big investments, can be shaped into smaller pieces, solving at the same time some technical issues. This allows a step-by-step investment and implementation with each step having a ROI case, providing justification of the investment. The company, although taking small steps, is doing so in the context of a journey toward a manufacturing infrastructure which meets the future business challenges. This will enable companies to be ready for the possible future business scenarios and to take advantage of adopting new technologies early. The critical elements are the selection of the improvement options, the identification of the right KPIs, the size and sequence of the steps, and last but not least, the fit of the future manufacturing vision with the possible future business landscape. Case Study 2 illustrates how this might work in action in a vaccine plant.

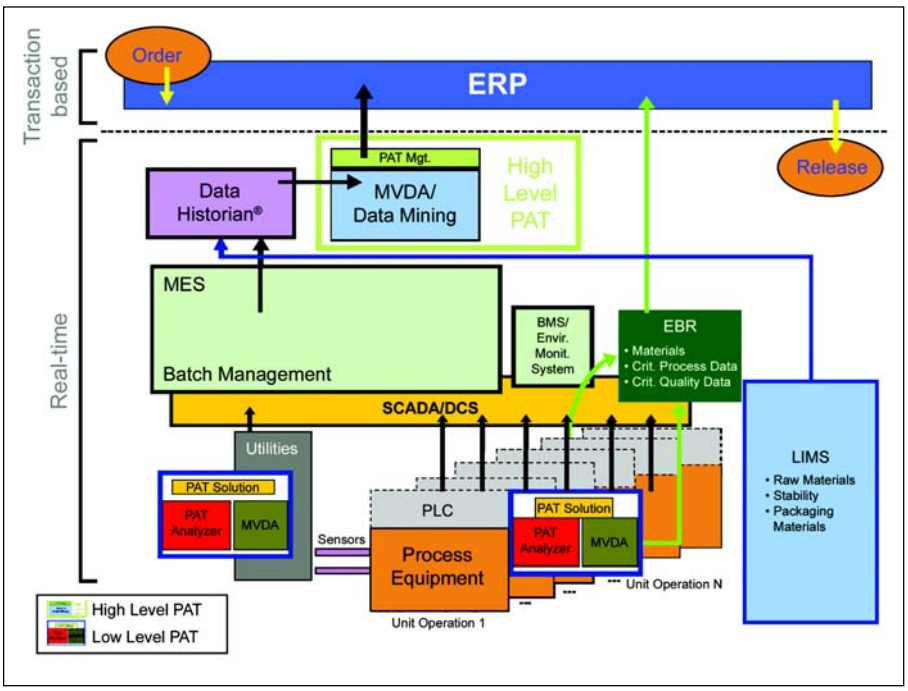


Figure 5. Manufacturing infrastructure scheme.

Manufacturing Infrastructure

Once they have chosen between different possible manufacturing visions and completed some scenario planning, companies will, of course, need to decide on the manufacturing and IT infrastructure that will be required for the chosen scenario. Decisions about the future architecture will differ between the various scenarios, and crucially between those with smaller size process equipment and larger scale manufacturing. As an example, Figure 5 outlines a manufacturing infrastructure scheme corresponding to scenario 2 of Figure 3. The PAT solution has interfaces to the process equipment, the process automation, and will take care of data collection from the process, eventually from extra real-time measurements (PAT Analyser) as well as data storage and retrieval. It consists also of an MVDA engine able to interpret quality data and translate this into control and correction actions. The high level PAT solution will combine various unit operations and will take care of the overall product release of the final product.

In general, the role of the quality management system will shift to the manufacturing floor and will be of more strategic importance, as it is essential for real-time product release. Greater integration of multi-disciplinary teams will be an important factor alongside the hardware and software. The quality management system will consist of a LIMS system and PAT systems (on unit and on line level). It will allow Production Performance Analysis (PPA). In turn, for faster time-to-market, a closer link between development and manufacturing is required that allows for continuous improvement. Figure 6 outlines the wider architecture that is needed. A central role will be occupied by knowledge management systems and data portals, but also by advanced data mining techniques. The

role of knowledge management systems and data portals will be essential for this change.

Conclusion

A combination of regulatory, market, scientific, and technological forces is likely to mean that pharmaceutical manufacturing will undergo rapid change in the next five to 10 years. Many companies are already investing in change projects, but they are often piecemeal and not accompanied by a clear manufacturing vision. The absence of such a vision also means that companies sometimes feel caught between 'big leap' and more incremental changes. In fact, incremental change is vital to achieve a longer term 'big leap.' But, in the absence of a manufacturing vision, companies find themselves with no roadmap. The consequence is that changes are made in relative isolation without maximizing their potential incremental contribution to longer term improvement or, worse, moving the company further away from the manufacturing it will need in the future.

We have shown how companies can use a range of tools – scenario planning, ROI analysis, KPIs – to construct such a roadmap to ensure changes are linked together, thereby avoiding piecemeal and sub-optimal change. There is a need for companies to more consistently align investment in IT and manufacturing with their vision of the manufacturing that will be needed in the future. In doing so, companies will be able to ensure that investments don't just deliver specific gains, but also help accelerate the company's progress toward longer term goals.

References

1. Innovation and Continuous Improvement in Pharmaceutical Manufacturing: The PAT Team and Manufacturing Science Working Group Report: A Summary of Learning, Contributions, and Proposed Next Steps for Moving Toward the "Desired State" of Pharmaceutical Manufacturing in the 21st Century. http://www.fda.gov/cder/gmp/gmp2004/manufSciWP.pdf.
2. Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach Final Report. Department of Health and Human Services, US Food and Drug Administration, September 2004. http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm#_Toc84065738.
3. The Royal Society, Personalised Medicines: Hopes and Realities,

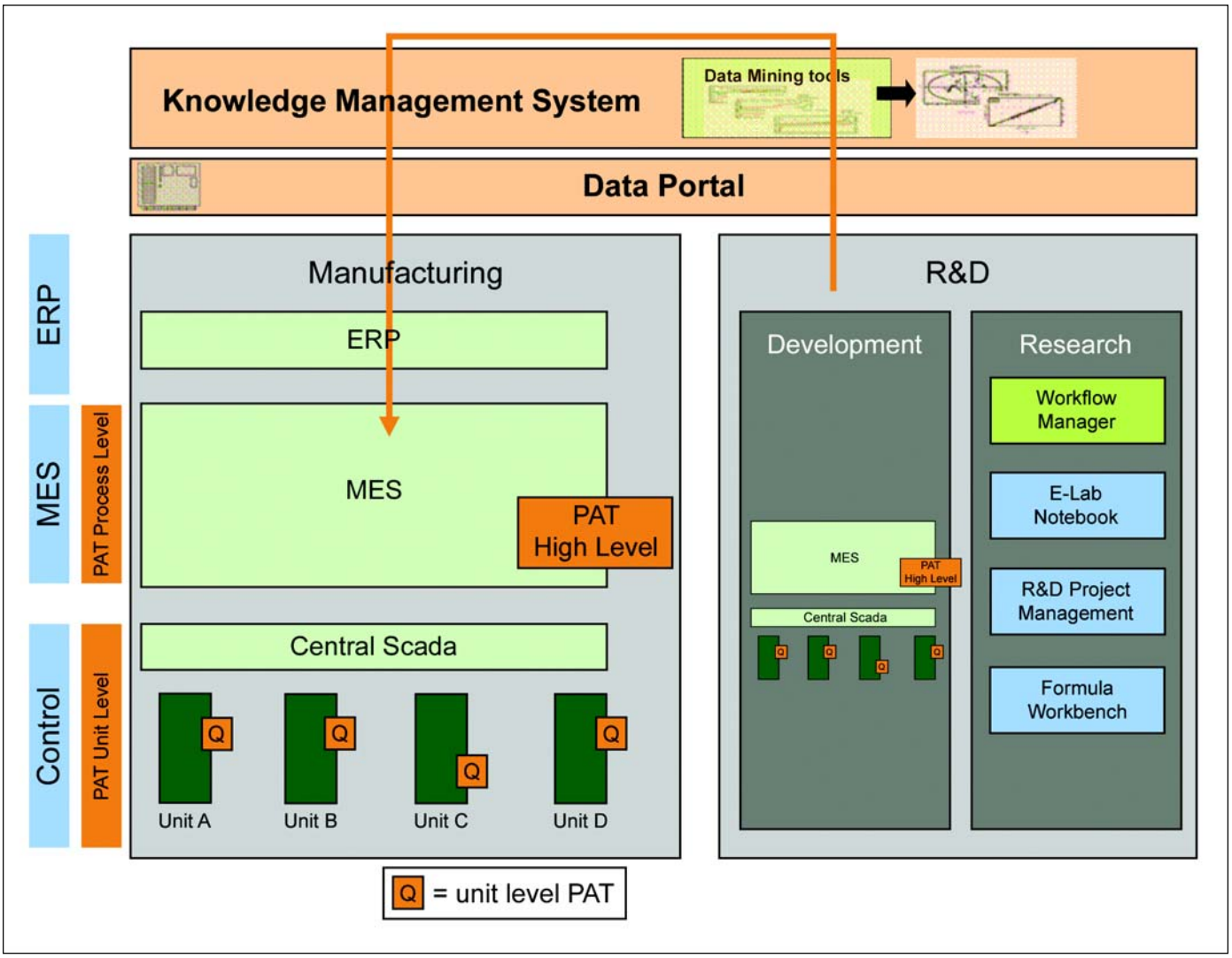


Figure 6. Tighter integration of development, manufacturing and knowledge to achieve continuous improvement.

press release, 21 September 2005, ref 18/05.
4. The Royal Society, Personalised Medicines: Hopes and Realities, September 2005, p 2.
5. ibid. p 1.
6. Quality Manufacturing: A Blockbuster Opportunity for Pharmaceuticals, Economist Intelligence Unit, 2005.
7. PAT Strategy: Islands of PAT to be Tied Together, Graham Cooke, European Pharmaceutical Review, issue 5, 2006.
8. Ibid.
9. Innovation Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products, US Department of Health and Human Services, Food and Drug Administration, March 2004.

About the Authors

Beatrijs Van Liedekerke is Associate Director at PriceWaterhouseCoopers, China. Van Liedekerke is a pharmacist and has a PhD in the pharmaceutical sciences. She has industry experience in the food, biotech, and pharmaceutical industries where she held positions in QA, QC, manufacturing, R&D, and customer relations. Over the last four years, she has been an adviser to companies on operational improvement, overall business optimization, and regulatory compliance. She can be contacted by e-mail at: beatrijs.vanliedekerke@cn.pwc.com.

PriceWaterhouseCoopers, Beijing Fortune Plz, 26/F Office Tower A 7, Dongsanhuan Zhong Rd. Chaoyang Dist, Beijing 100020, China.

Ingrid Maes is Senior Consultant in the Pharma Competence Center of Siemens A&D. She has an engineering background in the chemical and agricultural industries with a specialization in biotechnology. Through different positions at Siemens, Maes has a wide expertise in process analytical tools, multivariate data analysis, automation, and control of manufacturing processes in the food and feed, biotech and (petro) chemical sectors, as well as in the pharmaceutical industry. She can be contacted by e-mail at: ingrid.maes@ siemens.com.

Siemens AG HQ Pharma Competence Centre Pharmaceutics - Consultant Advanced Technologies, Nieuwe Wegl, B-2070 Antwerpen (Zwijndrecht), Belgium.

Exclusive On-Line Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Using a Process Description to Define Automation Needs for a Life Sciences Project

by Steve Murray, Amit Shah, and Dawn Marruchella

This article describes how a detailed Process Description (PD) can help to alleviate many of the pitfalls that are encountered in the automation of a life sciences process.

The Need for a Process Description

A detailed Process Description (PD) can help to alleviate many of the pitfalls that are encountered in the automation of a life sciences process, the majority of which are batch processes. Delivering a properly automated process solution on schedule and within budget can be challenging on most projects, even when requirements are well defined and re-work is minimal.

A properly structured PD with appropriate details can help the automation team write Functional Design Specification (FDS) documents that effectively achieve the following critical business goals:

- Gather together the knowledge and insights of laboratory science, process design, quality control, and pilot plant personnel into a single location.
- Translate this expertise into automation requirements that define how a product should be made consistently and repeatably in compliance with regulatory requirements.

A thoroughly reviewed and mutually accepted FDS allows the automation team to develop a highly modular specification and design structure. This modular structure can lead to a component-based automation software application that allows consistent reuse between plants and processes, improves built-in quality, and speeds software development, while minimizing the addition of cost and/or resources. Furthermore, modular software reduces testing, commissioning, qualification, and maintenance requirements.

Understanding the complete process requirements for a batch project allows the automation team to take their knowledge of automation control systems and the ANSI/ISA S88 standard for batch control[1] and apply it to the process in the most efficient manner. The resulting automation design not only meets the requirements for the current process, but also allows for future flexibility and follows a common set of standards across the project.

On the contrary, if the PD is poorly written without input from all relevant groups and lacks clear requirements, the auto-

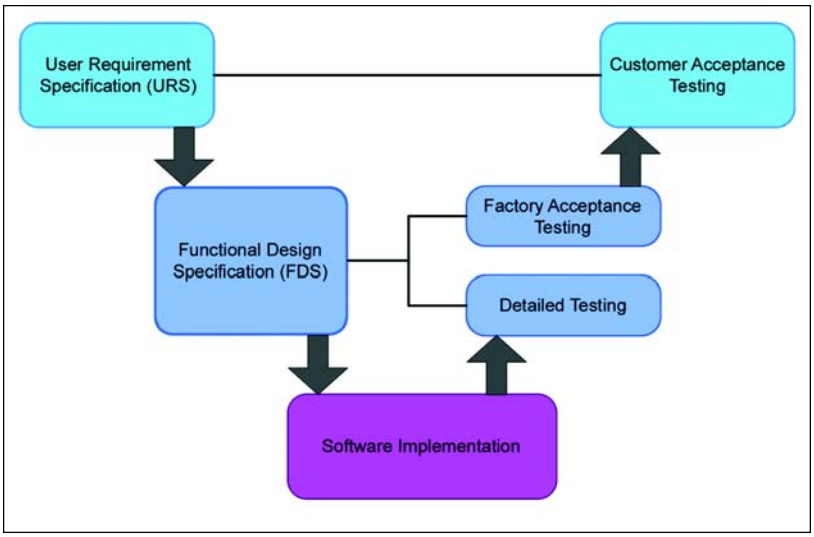


Figure 1. Basic GAMP "V".

mation team is forced to make assumptions, while writing the FDS documents. This typically leads to several iterations of the FDS documents with numerous communications back and forth or, worse yet, some details not being accounted for until much later in the project execution when changes are more painful and costly. In determining commonality across the project, missed details will cause greater problems. If sufficient time is not taken, the chance for success in meeting schedule, budget, and product quality demands and also in minimizing stress on personnel will be significantly decreased. Starting slowly at the beginning of a project will pay off many times over by reducing rework and speeding implementation. A deliberate start also will take advantage of the inherent interdependency among the many contributors.

This article is intended to serve as a guide for members of process design teams needing to communicate process automation requirements to their automation team. While the level of automation may be adjusted somewhat in the FDS portion of the project, there needs to be a documented handover of the process automation requirements and a defined process for communicating requirement changes that may occur after the PD is issued by the process design team to the automation team.

There is a misconception that if a PD is created, it must always be a "living" document that must be managed for the life of the system, using change control procedures. This is actually not the case - those familiar with GAMP Good Automated Manufacturing Practice Guide for Validation of Automated Systems[2] model will recognize Figure 1 as GAMP's basic framework for the specification and qualification of an automated system. This model addresses the lifecycle documents that need to be created, but it never details how to communicate the information required to generate these documents. A PD document is a very efficient and many times a necessary document to develop automation FDS. Depending on the company's needs, the PD may be maintained under change control as a living document or obsoleted by the FDS.

What is a Process Description?

Sometimes called a process narrative, a Process Description (PD) is a well organized, detailed account of what the process does and how it works that accompanies Process Flow Diagrams (PFDs) and Piping and Instrumentation Diagrams (P&IDs). One of the goals of the process description is to create a clear understanding between the process design team and the automation team about the process control requirements for a particular process or process area within a facility. PDs can serve as the origin of requested process changes if the document is maintained as an ongoing communication tool, and can serve many other roles in an organization. PDs have been successfully used in other industries to serve this purpose, but the challenge in the Life Sciences industries is to determine the role that the document serves in the project lifecycle (if any).

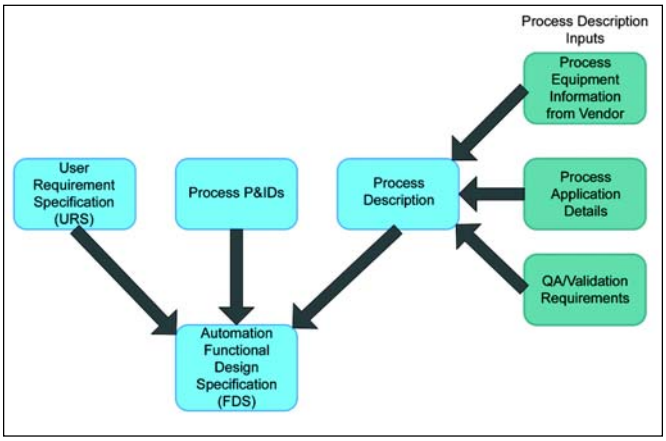


Figure 2. An optimal method to develop automation functional design specification.

Providing too much detail and/or making too many design assumptions in the PD can lead the automation FDS for that process or process area down a path that may not produce the best automation solution for the process. This frequently results in inadvertent grouping of sequences considered by the process design team to be similar, but that really have too many differences to be implemented as the same software element. It is best to let the process design team describe the process requirements and then let the automation team determine the best way to automate these requirements. It is important to note that the authors of this article do not wish for the term automation FDS to be confused with automation control system requirements that would normally be provided in a User Requirements Specification (URS).

A well written PD should contain elements that address, at a minimum, the following:

- objective
- reference documents
- overview of the process
- general process flow information
- general and specific equipment and instrumentation information
- auxiliary systems requirements
- sequence of operations
- continuous control requirements
- equipment scheduling requirements
- detailed narrative of the process describing (where applicable):
  - equipment states
  - equipment cleaning and sterilization requirements
  - sequencing requirements
  - normal operating conditions
  - abnormal operating conditions
  - input parameters
  - report parameters
  - critical parameters
  - alarms
  - operator interactions
  - process interlocks and permissives
  - time critical operations

An example of portions of a process description is included at the end of this article.

This information can all be provided in the User Requirement Specification (URS) documents called out by the GAMP standard, but this is generally an inefficient way to manage the process information. GAMP suggests, but does not dictate, that the content of the URS include an Operational Requirements section. The GAMP guide directs that "process descriptions or flowcharts may be included as appropriate." For a small project, the URS may be used to communicate all of the process requirements since the document in such cases is usually small and developed by a few people. For a large project, the process requirements are more complex; and maintaining and controlling the specifications as part of the system lifecycle can be an onerous effort. It can be inefficient to include process information since it is repeated in the functional design specification. As the functional design specifications evolve through the project and through the years of operation of the facility, there is a large amount of duplicated effort in maintaining the same information in both the FDS and the URS. The URS and the FDS together need to provide the basis for the acceptance of the system - and should contain a minimal amount of repeated information. Therefore, it is the authors' opinion that process requirements should be written in a Process Description document independent of the URS.

Although the process design team, who is responsible for developing the PD, may possess detailed knowledge of the S88 batch architecture, the PD should define little, if any, of its structure. The PD, along with the other inputs shown in Figure 2, are most likely sufficient to produce a detailed FDS. Typically, the PD is written by the process group using, along with the information provided by the equipment vendors, the process specific applications as well as input from the QA and validation groups. It also is important to provide for the involvement of QA and validation during PD since they have unique automation needs that need to be included as part of the requirements. For example, operator prompts that comply with 21 CFR Part 11 are clearly a validation requirement that many times fail to be noted as a requirement early in the project. Once the PD is written, the automation FDS is developed using the URS, PD, and the P&IDs as shown in Figure 2.

As PDs and other inputs are considered, the appropriate S88 architecture will evolve as a result of the FDS development process. The benefit of permitting the S88 architecture to evolve in this manner is that the automation team is likely to be more knowledgeable about the S88 model and its application to projects. A major benefit of such an evolutionary process is that software classes and templates can be created, tested, validated, and then re-used with minimal additional testing. Not only does this create a robust control solution, it creates a solution that will be easier to maintain in a validated state over time. Once completed, the FDS becomes the primary communication mechanism among the automation group members.

For additional information on the S88 standard and what an S88 batch architecture might look like, the authors suggest visiting the ISA (www.isa.org) or WBF (formerly known as the World Batch Forum) (www.wbf.org) Web sites where the various parts of the standard may be purchased and white papers on the standard can be downloaded, respectively.

Incomplete and/or ambiguous PDs often produce one of two scenarios: either they produce an ill-defined project that has costly changes or schedule delays; or they lead to lengthy discussions and/or incorrect assumptions during later phases of the project. The process of waiting for answers to questions, while creating the FDS can cause project delays and/or rework. Moreover, it can produce anxiety and frustration from within the end-user organization. Not only are end-users distracted from other tasks, but they also begin to question why the automation team cannot ask all the questions at once, and may call into question the value of the automation team.

Exception Handling Routines Vital

Many PDs provide a list of equipment capabilities as per the equipment vendor documentation describing how the equipment ***operates***. What's missing is how the equipment ***will be used*** for a particular process application. Furthermore, application related information should enhance the operational requirements with any operating parameters and the legal ranges that operators or batch recipe structures are permitted to modify.

Although it is necessary to include extensive documentation of the normal equipment operation, equipment exception handling and the conditions that constitute exceptions are equally important and must be extensively documented in the PD as well.

Exception handling can require input from multiple groups, including safety, process, quality, and maintenance. In a manual plant, exception handling is covered by the experience and judgment of the operations staff. However, when the facility is highly automated all exception scenarios, events, and conditions are handled automatically. Thus, abnormal situations must be identified and defined beforehand. Often the best opportunity to explore and document abnormal situations is during process Hazard and Operability (HAZOP) studies. In addition, the acceptance testing of automation configuration is generally focused more on normal operations and ill-defined fault scenarios can make it to the qualification process. Of course, correction of them at this point is much more costly and might concern the process owner that things may not be properly thought out and fully tested.

Include Global Requirements and Standards

In large automation projects, there are several common requirements and repetitive automation requirements that span multiple processing areas. These are sometimes referred to as "global" requirements. For example, equipment status tracking (e.g., clean, dirty, etc.), agitator operation, jacket temperature control, product transfer stations, etc., are likely candidates for developing standardized solutions. Where possible, these requirements should be grouped in a Global (project-wide) PD and then referenced by other PDs. For example, once a standardized jacket temperature control

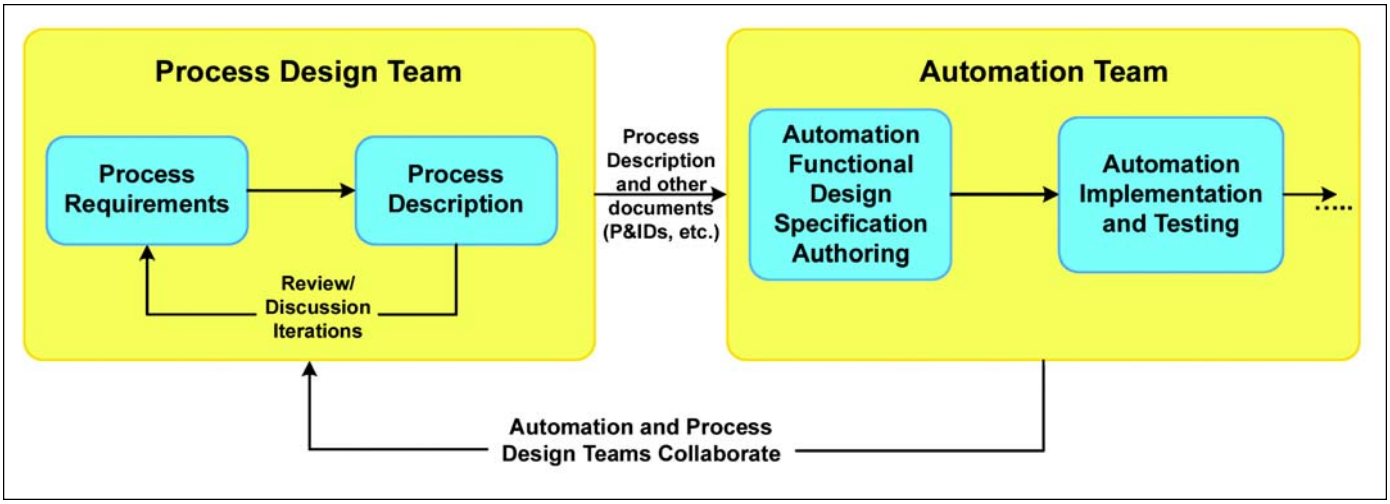


Figure 3. Collaborative and iterative process description development.

requirement has been defined in detail in the Global PD, the PD for fermentation would simply declare the start/hold/resume/stop of the jacket temperature control.

Another example is that almost every unit in a facility needs to perform a pressure test at some point in the process, whether it is prior to performing a sterilization or immediately before performing a pressurized transfer. A section in the Global PD can detail the requirements for performing a pressure test, including indication of what the automation should do in the event of a failed test. Area specific PDs would now only need to make reference to the Global PD when indicating the necessity for a pressure test that is the same as the global definition. Even where there is a special scenario, only the deviations from the general requirements will need to be detailed in the area-specific document. Defining global requirements also promotes collaborative effort and a mindset across the process areas to standardize wherever possible allowing for a cleaner, simpler automation solution.

Who Should Write a Process Description – and When?

A process description should be written by the process design team with the assistance of the automation team. It may be advisable to involve an automation team at this time if they have the background and skills to add significant value to the process - but most of the automation team's effort will be at the FDS phase. The automation team should provide details about the type of information required from the process design team using good PD examples. This will avoid re-work for the process design team and allow the project to stay on an accelerated time schedule.

The details of the intended process are often not entirely clear at the start of the FDS development phase. The goal is to minimize the need for the FDS author, a member of the automation team, to request clarifications from the PD author, a member of the process design team. This process is not only time-consuming for everyone involved, but the communication chain allows for miscommunications that can cause scope and content disputes at the point of system acceptance. Creating specifications about scenarios that are not required is undesirable. Change orders that result from misunderstandings are never well received and should be avoided. Figure 3 shows the desired document flow of the PD and where it fits into the project execution.

There are times when a Process Description may not be necessary for a life sciences project. If a project is small enough to cover all of the required details in a URS, then it may be enough documentation for the automation team to use for the FDS development. Furthermore, the automation team, who would be responsible for authoring the FDS, may work very closely within the same organization as the authors of the Automation and Process Requirements Specifications, thus, eliminating the PD need. The PD is a communication tool - if the communication can take place through ongoing interaction, then the PD would not provide as much value. In contrast, for large projects, the process requirements, automation requirements, and functional design specifications often do not come from closely integrated groups; therefore, there is usually a compelling reason for such a communication tool.

Where Does a PD Fit into the System Life Cycle?

A URS will be written to contain many general requirements of the system, but will probably not contain the detailed requirements of how the process is to operate. The detailing of the process requirements to the automation team will then require the supplemental PD to provide the basis for their FDS efforts. It is important to note that this document doesn't need to be maintained past the point where it adds value.

Remember that a PD is an excellent communications tool. Many organizations do not see the need to maintain the PD as a living document under change control. This is especially true if an FDS is prepared with a multi-disciplinary effort between Process Development, Automation, Validation, Quality Control, and Operations. Figure 2 illustrates that it is possible and practical to use P&IDs and associated process descriptions as source material for developing an FDS, while

still working within the recommended GAMP structure. This structure provides a good basis on which to build an S88-based structure that promotes modular design.

The concept of using the PD as a means to an end in generating a comprehensive FDS can be a challenging undertaking. The automation team will need to stay vigilant in ensuring that any evolutionary changes to the FDS are in line with the intentions of the process design team. These evolutionary changes can result from a number of different origins, including inconsistent PDs across multiple areas; simple errors in the PDs themselves; or enhanced software modularity goals. While the PD may be approved, an analysis by the automation team may reveal that the operation of equipment like filtration and Clean-In-Place (CIP) skids may be defined differently in different areas for no reason other than the fact that they were authored by different process design team members at different times. Similarly, the automation team may seek to reduce the maintenance and training burden of the operations staff by standardizing the functionality of more common functions, like jacket temperature control. It is in this respect that the automation team can add great value to the project.

The PD must set the expectations for the level of automation. There are likely to be critical bottlenecks in the process that need to be highly automated to attain maximum product throughput. Generally, bottlenecks represent "non-negotiable" portions of the automation process. These should be articulated so the automation team has a clear picture of the production requirements to sustain the performance of the process.

While scope can certainly be reduced during the generation of the FDS documents, it may be beneficial to specify up front that certain automation is not required to save part of the budget for unknowns yet to come.

What Comes After the PD?

Once the PD is handed off to the automation team so that they may write the FDS, the true design of the automation for the process begins. For this reason, it is important for the process engineers to note that if there is a controls requirement, whether it is an alarm, a report parameter, an operator message, or an interlock, it is essential that the requirement is included in the PD. The PD, coupled with the P&IDs and URS documents are the *basis for the automation design of the process,* and as such should be the basis upon which the completion of the automation process is measured.

There is significant benefit in having automation-focused individuals involved at this point to interpret the PD and transform it into a structured FDS that allows for traceability through a modular design and implementation of the application software. What makes this a desirable and workable solution is that the FDS is best created by those most familiar with the application of each process control requirement within the integrated software application solution. This group generally includes both the application software supplier and the automation engineers within the end-user organization.

Prototyping activities and design guideline documents for the project are among the first deliverables to be developed. The prototype and resulting guideline documents are an important part of the project standards. Once approved, the design guideline documents and the comments from the prototyping effort are released for implementation of code. A change to the requirements at this point in the life cycle results in an increase in cost and more importantly, a delay in schedule. Depending upon the change, other process areas also may be affected. For example, a change to the CIP Skid has the potential to affect all of the units for which it cleans.

Upon completion of implementation, internal testing is done prior to performing the software acceptance testing. When changes to requirements are made at this stage, not only are FDS documents affected, but automation configuration also must be re-worked, test protocols rewritten and re-executed, or existing tests re-executed prior to code release. The increase in cost and schedule due to changes in automation requirements continues to grow exponentially as the project life cycle progresses.

Sample Excerpts from a Fermentor PD

In an effort to further explain the level of information that should be contained in a PD, some selected sample information from a Fermentor PD is included. These are intended to illustrate the level of detail appropriate to the PD and are not intended to be complete or depicted as the only method of developing the PD, hence, some of the sections only show outline items and don't include detailed information. Additionally, some of the tables are not intended to be complete (for example, instrumentation and equipment tables), but are there to provide enough information to provide general guidance.

Table of Contents

1 Introduction

1.1 Objective

The ABC Manufacturing Facility will be designed to handle the fermentation and purification of the process for types 1, 4, and 9 of the XYZ product. The purified product will be shipped to the HIJ facility for finishing. The scope of this project covers only the fermentation and purification of those products mentioned above. Standard operating procedures will be followed for control of the process and equipment. The scope of this document covers the fermentor portion of the process.

1.2 Reference Documents and Drawings

2 Process Overview

The fermentor area consists of a series of operations that are either automated or manual. In either case, the operators initiate the sequences, which include the following:

- Manual Set-Up Fermentor
- Initialize Fermentor
- CIP Fermentor
- Pressure Test Fermentor
- SIP Fermentor
- SIP Fermentor Sample Port
- Inoculate Fermentor
- Fermentation
- Sample
- Fermentor Transfer Out

There are four seed fermentors (45L, 150L, 1,000L, and 2,750L) and one production fermentor (8,000L). Media is transferred into the fermentors using bags for the two smallest seed fermentors and from the media tanks through the media filters for the two larger seed and production fermentors. Acid and Base tanks supply the production fermentor as does a Nutrient tank as shown in the flow diagram in the next section. The three smallest seed fermentors each have sparge lines for control of dissolved oxygen and the largest seed fermentor and production fermentor have both upper and lower sparge lines. Upon completion of fermentation, the production fermentor transfers its product to the harvest tank for further processing.

2.1 Process Flow Diagram

3. Equipment Information

3.1 Equipment

The fermentation area includes the equipment shown in Table A:

Equipment	Description
SFE1001	45L Seed Fermentor
SFE1002	150L Seed Fermentor
SFE1003	1,000L Seed Fermentor
SFE1004	2,750L Seed Fermentor
PFE1000	8,000L Production Fermentor
AG1001	SFE1001 Agitator
AG1002	SFE1002 Agitator
AG1003	SFE1003 Agitator
AG1004	SFE1004 Agitator
AG1000	PFE1000 Agitator
VF1001	SFE1001 Vent Filter
VF1002	SFE1002 Vent Filter
VF1003	SFE1003 Vent Filter
VF1004	SFE1004 Vent Filter
VF1000	PFE1000 Vent Filter
PU1001	SFE1001 Additive Pump
PU1002	SFE1002 Additive Pump
PU1003	SFE1003 Additive Pump
PU1004	SFE1004 Additive Pump
PU1000	PFE1000 Additive Pump

Table A.

3.1.1 Equipment States

The equipment listed below will always be in one of the following states:

Dirty: equipment has completed processing operations, or has just been returned from being out of service or its time in the clean or steamed state has expired.

Clean: equipment has successfully completed CIP operations.

Steamed: equipment has successfully completed SIP operations.

Out of Service: equipment is currently out of service and must undergo cleaning/steaming upon return to service for use.

3.1.2 Cleaning and Sterilization Requirements

Refer to the Common Process Description for Cleaning and Sterilization requirements for all vessels.

3.1.3 Equipment Scheduling Requirements

3.2 Instrumentation

Table B shows the instrumentation for the fermentors.

Tag Name	Description	Operating Range
Production Fermentor PFE1000		
AI-1000-001A AI-1000-001B	Dissolved Oxygen Probes	0 – 100%
AI-1000-004A AI-1000-004B	pH Probes	0.00 – 14.00
FSH-1000-003	Foam Detector Switch	On/Off
PIC-1000-005	Vessel Pressure	0 – 50 psig
TIC-1000-001	Vessel Temperature	0.0 – 200.0°C
TI-1000-004	Jacket Inlet Temperature	-35.0 – 250.0°C
TI-1000-006	Jacket Outlet Temperature	-35.0 – 250.0°C
WI-1000-001	Load Cell Weight	0.0 – 10,000.0 kg
Seed Fermentor PFE1001		
Seed Fermentor PFE1002		
Seed Fermentor PFE1003		
Seed Fermentor PFE1004		

Table B.

3.3 Auxiliary Systems

The fermentors require auxiliary support as indicated in Table C:

Support Item	Operating Conditions
Carbon Dioxide	38 – 40 psig
Clean Air	35 – 40 psig
Clean Steam	35 – 40 psig
Chilled Glycol	-50.0 – -35°C
Instrument Air	100 – 110 psig
Nitrogen	30 – 35 psig
Oxygen	30 – 35 psig
Plant Steam	65 – 70 psig
Hot WFI	90 – 95°C

Table C.

4. Sequence of Operations

4.1 Fermentor Clean-in-Place (CIP)

4.2 Fermentor Pressure Test

4.3 Fermentor Steam-in-Place (SIP)

4.3.1 Operating Requirement

This operation may run alone or as part of larger recipe.

4.3.2 Sequential Flow Diagram

See Figure 4.

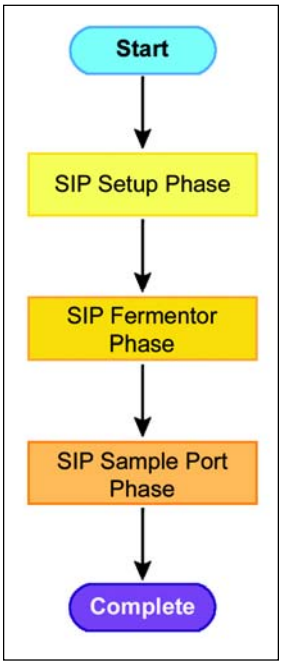


Figure 4. Recipe operation sequencing details.

4.4 Inoculation

4.5 Fermentation

5. Phase Sequences

5.1 Sample Bottle Sterilize-in-Place (SIP)

The operator is prompted to attach sample bottles to the sample port. Bottle connection is SIP'd and valves are returned to pre-SIP condition.

This sequence can not be run until a successful SIP of the Fermentor has been completed.

There are no time critical operations associated with this sequence. However, once the bottle has been successfully SIP'd, the bottle must either be used or SIP repeated before 24 hours has elapsed.

There are no critical alarms which need to be reported in association with this sequence. Successful completion of the sequence will indicate a successful SIP.

5.1.1 Input Parameters

Parameter specified in recipe (may change between batches).

Recipe Parameter	Typical Value	Allowable Range
Time to achieve SIP temperature	60 minutes	50 – 70 minutes
Initial temperature	100°C	100 – 110°C

Table D.

5.1.2 Report Parameters

Parameter to be recorded when temperature is achieved.

Reported Parameter
Time to achieve SIP temperature

Table E.

5.1.3 Operating Parameters

Parameter available for adjustment – not in recipe.

Operating Parameter	Typical Value	Allowable Range
Maximum time to achieve SIP temperature	15 minutes	10 – 30 minutes

Table F.

5.1.4 Abnormal Operations

Abnormal Operation Requirements

Exception Handling	Required Action
HOLD Functionality	Close clean steam supply valves. Open trap valves to vent pressure.
RESUME Functionality	Open clean steam supply valves. Restart timer. If temperature at any trap falls below 121°C, start timer from zero once TIs are at temp.
ABORT Functionality	Discontinue vessel jacket temperature control. Release vessel pressure. Close all steam valves and appropriate process valves as necessary.

Table G.

5.1.5 Sequential Flow Diagram See Figure 5.

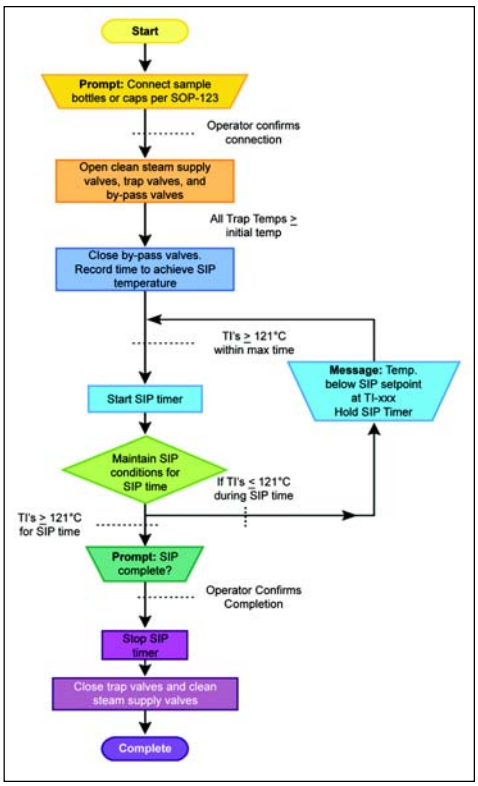


Figure 5. Phase Operation sequencing details.

5.2 Fermentor Set-Up

5.3 Fermentor Pressure Test

5.4 Fermentor SIP

5.5 Fermentor CIP

5.6 Fermentor Inoculation

5.7 Fermentor Transfer Out

6. Continuous Control

6.1 Pressure Control

The pressure in the fermentor is monitored using a pressure transmitter and maintained using a backpressure control valve. There are different modes of operation for Fermentation, Transfer, Sterilize-in-Place (SIP), Cool-Down, and Vent.

Operating Mode	Required Action
Fermentation	Control vessel pressure at Fermentation Pressure (psig)
Transfer	Controls vessel pressure at recipe-specified value (psig)
SIP	Controls vessel pressure at SIP Pressure (psig)
Cool-Down	Controls vessel pressure at Cool-Down Pressure (psig)
Vent	Vessel vented – no pressure control

Table H.

Parameter required to be available for adjustment – may be written by recipe as well.

Operating Parameter	Typical Value	Allowable Range
Fermentation Pressure	4 psig	2 – 8 psig
SIP Pressure	15.5 psig	12 – 18 psig
Cool-Down Pressure	5 psig	3 – 7 psig

Table I.

6.1.1 Interlocks and Permissives

There are no interlocks or permissives associated with the fermentation pressure control module.

6.2 Temperature Control

6.3 Antifoam Control

6.4 pH Control

6.5 Dissolved Oxygen Control

6.6 Agitator Control

Summary

Too little, incomplete, or incorrect detail in the PD frequently leads to developing an FDS that ends up requiring costly and time-consuming re-work as new or conflicting requirements are included or resolved. A properly structured PD with appropriate details can help an automation team write FDS documents that effectively translate client process information into automation requirements that define how a product is made consistently and repeatably, while complying with relevant regulatory requirements.

Finding the balance is critical in ensuring a predictable automation project. The PD should focus on detailing ***what*** the control requirements for the process are so that the FDS can define ***how*** the automation will accomplish meeting these requirements.

Good communication between the authors of both documents is imperative throughout the development and duration of the project, with the automation team providing consultative inputs to the PD and the process design team doing the same during the development of the FDS. Working collaboratively ensures mutual understanding of the process and the automation which will reduce the risk of costly rework and unnecessary frustration by the members of both the automation and process design teams as a whole. In the end, the project will be successful and provide a positive experience for all.

References

1. Instrumentation, Systems, and Automation Society (ISA), ANSI/ISA-S88.01-1995: "Batch Control Part 1: Models and Terminology," 1995.
2. *GAMP® 4, Good Automated Manufacturing Practice (GAMP®) Guide for Validation of Automated Systems*, International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001.

About the Authors

Steve Murray is a Senior Principal Engineer in the Life Sciences Group at Emerson Process Management in Austin, Texas. Murray has more than 14 years in process automation experience, including 11 years of experience in the execution of projects for pharmaceutical/biotech manufacturing facilities. Murray has been the automation lead on large projects and has been involved in all stages of design and deployment of the automation system ranging from consultation on software architecture to start-up support. He

can be contacted by e-mail at: Steve.Murray@EmersonProcess.com.

Amit Shah is a Principal Engineer in the Life Sciences Group at Emerson Process Management in Austin, Texas. He has more than 13 years of progressive experience in life sciences and information technology industries, including process development/manufacturing improvement, automation design, IT consulting, and academic research in team lead and individual contributor roles. Shah holds a BS/MS in chemical engineering and an MBA. He can be contacted by e-mail at: amit.shah@emersonprocess.com.

Dawn Marruchella is the Batch Product Manager for Emerson Process Management in Austin, Texas. With more than 11 years of combined experience, Marruchella's background includes seven years of work executing batch automation projects for the life sciences industry. Marruchella has provided technical leadership for several automation projects, beginning with front end engineering efforts and continuing throughout project execution and on-site support. She can be contacted by e-mail at: dawn.marruchella@emersonprocess.com.

Emerson, 12301 Research Blvd., Research Park Plaza, Bldg. III, Austin, Texas 78759.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Eight Steps to PAT: Using the Design for Lean Six Sigma Toll-Gate Process as Best Practice

This article outlines an eight-step six Sigma toll-gate approach to PAT implementation.

by Bikash Chatterjee and Jeremy Green

Overview

The FDA's recent guidance regarding Process Analytical Technology (PAT) offers the pharmaceutical and biotech industries an unprecedented opportunity to leverage hard-won experience with scientific inquiry and innovation. However, the leap to PAT is significant for even the most rigorous development program. Many aspects of Six Sigma, including its use of statistical tools and its phase- or toll-gate approach to project management, can facilitate and accelerate a PAT initiative. Rather than advocating company-wide Six Sigma adoption as a prerequisite to effective PAT implementation, an eight-phase Design for Lean Six Sigma approach is recommended that can be used on a project-by-project basis.

Define - What is the problem? How are we failing to meet customer requirements? What is the process that produced the problem? What are the objectives of the project? What is the project plan?

Measure - What are the critical process performance metrics? What are they key process output variables (KPIVs)? What data needs to be collected?

Analyze - What is the root cause(s) of the problem? How can the root cause be verified? What are the key process input variables (KPIVs) that affect the KPOVs?

Improve - What is the best solution to the problem? How can the solution be verified? How can we optimize the KPIVs to yield KPOVs at desired levels? How can we verify and validate our results? Do improvements result in increased customer satisfaction?

Control - How can we hold the gains (standardize, monitor, and continue to improve)?

Figure 1. The Six Sigma DMAIC model.

Introduction: The Shift from Product Control to Process Control

Prior to 2002, regulatory oversight focused primarily upon adherence to pre-defined procedures, record keeping, and an audit trail as a means for ensuring product safety and efficacy. Due to the emphasis on oversight control, most firms would 'lock-down' their processes and control methods once process validation was complete. Product quality was achieved through off-line inspection, rather than through identifying, understanding, controlling, and optimizing critical process parameters. The FDA reinforced this mindset by requiring regulatory pre-approval before any changes could be made to the process. The FDA Modernization Act of 1997 initiated a change in policy and thinking that culminated in the release in 2002 of the guidance document *Pharmaceutical cGMPs for the 21st Century - A Risk Based Approach*. To streamline the regulatory approval process and enhance patient safety, this document proposed a shift to a science-based compliance model, integrating the disciplines of quality, safety, and risk management.

Since 2002, the FDA has released guidance documents on risk-based inspections, Part 11 electronic records and signatures, quality systems approach to pharmaceutical cGMPs, and

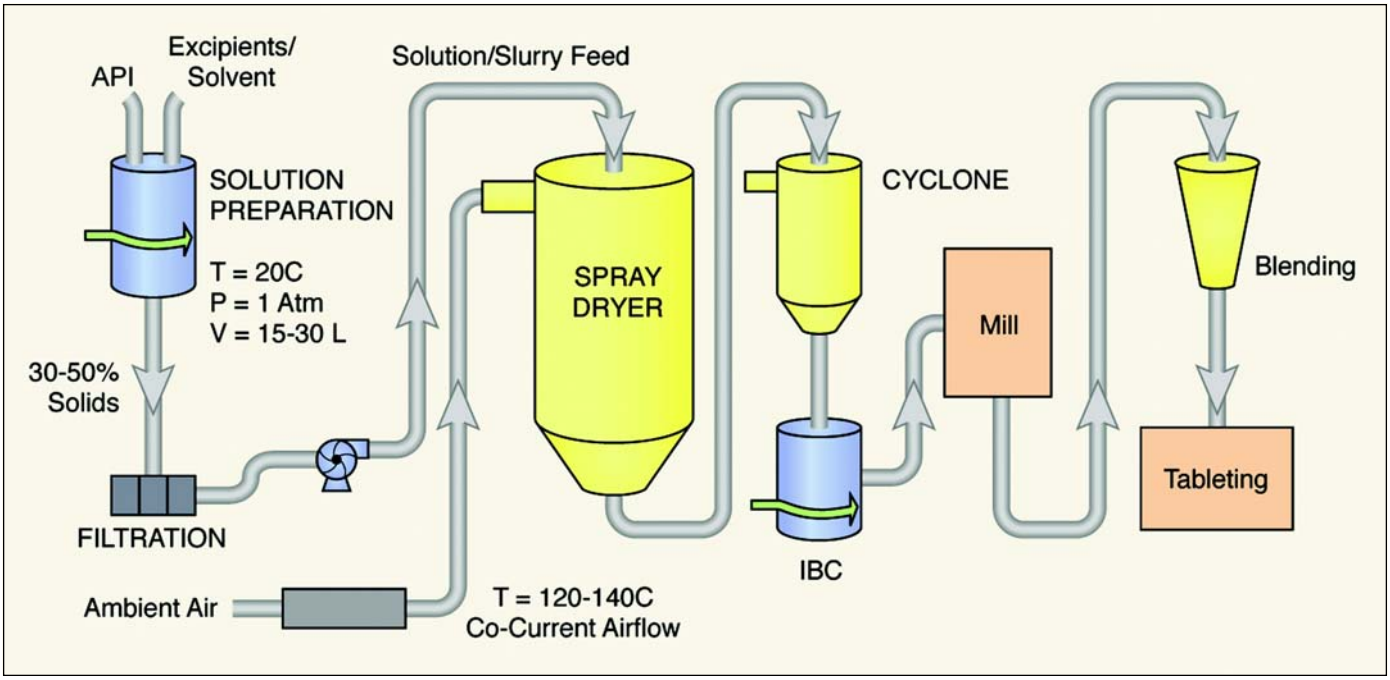


Figure 2. Controlled release tablet process flow.

Process Analytical Technology (PAT). The FDA was not the only regulatory body to recognize this need and solicited input from its counterparts in Canada, Europe, and Japan, and from industry and academics worldwide. Several key guidance documents from the International Conference on Harmonization (ICH), ICH Q8 (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and the forthcoming ICH Q10 (Quality Management) have become the *de facto* standard for transforming organizations that aspire to the highest degree of scientific rigor in the product development process. These documents comprise the basis for shifting manufacturing and regulatory philosophy from inspection and oversight to managed risk: a scientific approach capable of providing a higher level of product quality assurance.

Six Sigma and PAT

In September 2004, the FDA issued its final guidance, "*PAT: A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*." The fact that the guidance extends beyond a pure hardware solution underscores the Agency's desire to shift product quality assessment away from a product-centric approach, based on inspection and final testing, to one that is more process-centric and built upon understanding the variables that affect overall product quality. Process Analytical Technology (PAT) represents the culmination of a true process-centric quality system. Unfortunately, the industry has had difficulty embracing the total vision for PAT, partly because of its radical departure from historical methods of process and product development, and partly because of the lack of a definitive implementation model.

A criticism leveled at some PAT implementations is that efforts have focused on the application of on-line analytical technology (as a replacement for off-line laboratory testing), rather than on understanding control and reduction of variation.[1] In other words, the focus has been on the measurement, rather than the improvement of product quality. Statistical tools for characterization and optimization of manufacturing processes have been quietly in use in industry for more than 50 years although often confined to use by corporate statisticians. A renaissance in the more widespread use of industrial statistics by non-statisticians came with the advent of the improvement methodology of Lean Six Sigma in the mid-1980s.[2] A search of the PAT literature reveals an emphasis on the use of statistical tools, particularly multivariate methods.[3, 4, 5] However, the Lean Six Sigma approach to projects provides many advantages over isolated use of statistical tools. Among those advantages are:

1. selection of limited scope improvement projects, according to verified bottom line cost savings and increased customer satisfaction, achievable in two to six months

2. use of cross-functional teams led by a Six Sigma Black Belt (not a degreed statistician although trained in the use of statistical tools)

3. sponsorship of projects by a corporate executive champion, whose role is to remove political, financial, and other barriers that stand in the way of the team's success

4. Structuring the project in phases or stages, with each phase having defined statistical and lean tools, and objective criteria and metrics for the success of each phase. The most common approach is known by the acronym DMAIC; which stands for Define, Measure, Analyze, Improve, Control.

5. Toll-gate review meeting at the end of each phase. During this meeting, the team presents progress to date to members of senior management. If the team pays the "toll" by meeting the criteria and metrics for the phase, management raises the "gate" and allows the team to move to the next phase.[6]

The improvement methodology of Six Sigma provides an effective framework for the process characterization and optimization required by PAT that is superior to the use of statistical tools in isolation. A company-wide conversion to Six Sigma and its requirements for significant cultural change is not required. A less resource-intensive alternative is to use a Six Sigma project structure and associated statistical tools to characterize, control, and reduce process variation to achieve more consistent product quality. It is the authors' opinion that a phased Six Sigma toll-gate approach to product and process improvement significantly enhances and accelerates PAT implementation.

Based upon an actual PAT deployment initiative facilitated by Pharmatech Associates, the methodology employed and challenges encountered in the course of a PAT implementation project for a business unit of a major pharmaceutical company will be presented

Business Problem

The business unit had identified a number of improvement opportunities in its manufacturing process flow at one of its solid dosage manufacturing plants. The product was a controlled-release tablet which utilized a high molecular weight polymer to control the diffusion of the drug. The release profiles of the drug had been inconsistent since its market introduction two years previously resulting in rejected lots and a higher than desirable incidence of stage two dissolution testing. The inconsistent performance presented a potential regulatory risk to the product unless the variable dissolution performance could be addressed. In addition, the product demand was growing and the yield impact contributed to an erosion of plant capacity causing missed shipments and lost revenue to the business unit. Based upon projections there would be insufficient capacity to meet next year's demand.

A series of characterization studies was initiated using orthogonal experimental designs, evaluating API, granulation and compression parameters to identify the key parameters which affect dissolution performance. The investigation identified the root cause as periodic over-mixing of the lubricant during the final blending step, resulting in more hydrophobic surface properties. The inconsistent mixing performance was ultimately attributed to varying raw material properties, in particular particle size distribution, due to alternate lubricant suppliers. This source of variation was addressed through the establishment of a particle size distribution specification. In addition, only suppliers that demonstrated a process capability greater than 1.0 against the specification were qualified for the process.

Faced with the looming regulatory risk and capacity shortfall, management decided to initiate a PAT program to determine if the inconsistent product performance issue could be addressed through the use of in-line analytical measurements and closed loop control. The decision was made to deploy a PAT team to implement improvements with the objective of eliminating or significantly reducing process instability.

Tablet Lot	Percent Lubricant	Comment
Lot A	1.58	Control Space Lot
Lot B	1.68	Control Space Lot
Lot C	1.77	Control Space Lot
Lot D	1.54	Control Space Lot
Lot E	1.60	Control Space Lot
Lot F	1.44	Control Space Lot
Lot G	1.46	Control Space Lot
Lot H	1.63	Control Space Lot
Failed Lot 1	4.62	Failed L1 Dissolution
Failed Lot 2	6.48	Failed L2 Dissolution
Failed Lot 3	3.58	Failed L1 Dissolution
Failed Lot 4	5.44	Failed L2 Dissolution

Table A. Lot-to-Lot tablet lubricant content.

Plant Process Flow

The process flow for manufacturing is shown in Figure 2. The major unit operations are compounding (API addition in solution), granulation, milling, blending, and tableting. Given the results of the root cause analysis exercise the project focused upon the final blending step for the PAT project**.**

PAT Team

To deploy the project, the business unit established a PAT project team that consisted of experts from across the business unit, an outside pharmaceutical consulting firm, and an automation supplier. Although they were not a formal Lean Six Sigma organization, the pharmaceutical company had experience using many of the Lean Six Sigma statistical tools. The PAT team decided to apply the Six Sigma structure to the project from the outset because of the perceived advantage of a toll-gate approach with its built-in checks and balances. The Six Sigma approach allowed the team to clearly articulate success metrics for the individual stages of the project, as well as for the project as a whole, and align the project with current business objectives and strategy. The toll-gate approach, with its use of incremental success metrics, was instrumental in garnering senior management support from across the organization throughout the project. The team's first task was to define the deliverables and ensure consistency with current business and regulatory objectives. As described earlier, the plant was suffering from a capacity shortfall. The team met and summarized the situation as follows:

1. At the current manufacturing rate, the inconsistent tablet dissolution profile was costing the company $20 million on

an annual basis, not including the cost of poor quality associated with handling rejected material.

2. Rejected lots needed to be reduced to no more than 5% in order to recover the necessary manufacturing capacity for the coming year.

3. Estimated cost to the business unit due to dissolution failures or Stage 2 testing requirements was approximately 8% of the standing Work-In-Process (WIP) cost.

Based upon this assessment, the team determined it was appropriate to proceed with the PAT project. It is important to note that the objective in this case, from a business perspective, was not to replace the quality overhead associated with the tablet release, but rather to prevent the loss of product due to poor dissolution. This greatly simplified the initial regulatory strategy for the project, while leaving the door open for a future filing to replace product release testing with an in-process control strategy.

Six Sigma or Design for Six Sigma?

The team explored several models to evaluate the application of Six Sigma to the project. The classic Six Sigma DMAIC model provides a good framework for objective scientific inquiry and is typically used to improve existing processes (and products). However, the team decided that Design For Lean Six Sigma (DFLSS), with its focus on the development of new products and processes, would be a more appropriate approach for the PAT project. Subsequently, the team evaluated several of the current DFLSS Models as alternatives to the classic DMAIC model. DFLSS models provide a structured, phased approach to the design of a product, process, or service with Six Sigma Quality (target of 3.4 defects per million opportunities) and efficiency as key design criteria. Risk management is easily incorporated in the approach, as

DMADV	IDOV	DCOV
Define - What is the new process, product, or service? Why is it needed?	**Identify** - What are the needs and requirements of the customer?	**Design** - What are the needs and requirements of the customer?
Measure - What are the customer requirements? How do we translate these into design requirements?	**Design** - How do we translate customer needs and requirements into a product design?	**Characterize** - How do we translate customer needs and requirements into a product design? What are the key process input variables (KPIV) that affect customer requirements (KPOV)?
Analyze - What are the design alternatives? How do we select the best design concept (High Level Design)?	**Optimize** - How can we optimize the design to minimize variability and meet customer requirements?	**Optimize** - How can we optimize the design (KPIV) to minimize variability and meet customer requirements (KPOV)?
Design - What is the design realization (Detailed Design?)	**Verify** - How do we verify the design meets customer requirements?	**Verify** - How do we verify the design meets customer requirements?
Verify - How do we verify the design meets customer requirements?		

Figure 3. Lean DFSS models.

Failure Modes and Effects Analysis is a standard DFLSS tool. Integration of DFLSS with PAT answers the criticism of some current PAT implementations that focus too much on on-line analytical instrumentation rather than on the sources of process and product variation. This DFLSS toll-gate approach to PAT provides the additional advantage of a set of measurable success criteria for completion of key milestones within each phase of the process so the "gate" can be closed. Comparison of progress with such criteria provides objective evidence of incremental team success (that can be celebrated and communicated to the rest of the organization) and helps prevent team self-delusion. The DFLSS models[7] under consideration were Define, Measure, Analyze, Design, Verify (DMADV), Identify, Design, Optimize, Verify (IDOV), and Define, Characterize, Optimize, Verify (DCOV) - *Figure 3*.

Six Sigma PAT

In a review of the literature and with the recommendation of the pharmaceutical consulting firm, the team decided to use the DCOV DFLSS model with its focus on process characterization and optimization. The team expanded the DCOV roadmap into the following eight phases: Identify, Characterize, Define, Optimize, Measure, Automate, Verify, and Validate. The modified DCOV project management approach allows the business to make the best possible decisions with the available data and resources. The purpose behind each step of the eight-phase process is as follows:

1. **Identify:** clearly identify key elements of the project, including: regulatory strategy, regulatory commitment to Key Process Output Variables (KPOVs).

2. **Characterize:** what are the Key Process Input Variables (KPIVs) that have been characterized as they relate to the KPOVs?

3. **Define:** what is the defined design space for the process?

4. **Optimize:** what is the control space that defines the allowable KPIV levels in order to maintain the process within the design space?

5. **Measure:** what analytical solutions are possible surrogates for the existing offline measurement systems?

6. **Automate:** what control solutions can be applied to leverage?

7. **Verify:** prepare a proof-of-concept, process model.

8. **Validate:** complete the IQ, OQ, PQ, method validation and comparability study.

The PAT model adopted is shown in Figure 4.

Within each of the phases, there are a set of deliverables that must be completed to ensure all project requirements are met. Each will be discussed as follows:

Identify

In the identify phase, the PAT team is tasked with determining the design criteria for moving forward with the PAT strategy. The key process parameters, such as API physical characteristics, granulation process/control, and compression force/tablet hardness had previously been determined not to be the source of dissolution variation, leading the team to focus on the blending step. On the process side, the team developed a flow chart to identify the Process Input Variables and the Process Output Variables to design into the PAT solution. The input variables for the blending process identified were as follows:

1. Granulation Particle Size Distribution (PSD)
2. Mixing Time
3. Intensifier Arm
4. Lubricant PSD
5. Lubricant concentration

The process utilized a 60 cu.ft. mixer. The Chemistry, Manufacturing, and Controls (CMC) commitment during the original drug filing was to mix for five to 15 minutes, at a mixing speed of 10 rpm with the intensifier arm on. The KPOVs filed in the NDA for this step were content uniformity and tablet dissolution at two, four, and eight hours. The specification was 10 to 20%, 21 to 60%, and 61 to 100% respectively for these time points. The team determined it would use the tablet dissolution, API content uniformity, and concentration of lubricant as benchmarks for evaluating the content uniformity of the lubricant and the mixing effectiveness during that stage of the process. The regulatory strategy initially focused on establishing a control range within the NDA commitment. Since PAT focuses on a feedback control architecture, the intent was to establish a scientifically rigorous comparability data set using the optimized control range, then steer the target metrics for PAT automation to the same endpoints.

At this and subsequent phases, success metrics were established. Progress and metrics were presented to management at a toll-gate review meeting with management's charter to give the team approval to move to the next phase or to take additional action to resolve any open issues. For any open issues, the team would submit a formal corrective action to get management's approval to move to the next phase. This process continued through the subsequent seven phases.

Characterize

A retrospective review of the process development data indicated that there was no evaluation of the impact of granulation PSD or lubricant PSD. Lubricant concentration was evaluated, as was mixing time. Neither evaluation used an orthogonal experimental design; hence, the data could not be regressed. The development data evaluated 1% and 2% lubricant concentrations. Based upon this development work, the significant KPIV identified was mixing time with the KPOVs being tablet appearance and dissolution. Tablet appearance was representative of the tablet compression process. A final concentration of 1.5% was chosen.

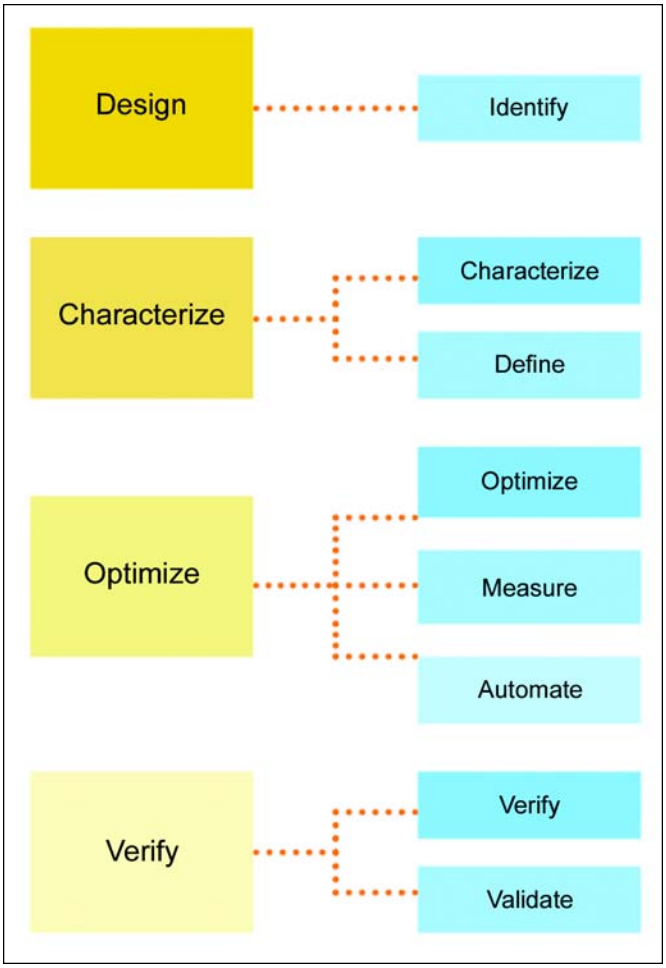


Figure 4. Design for Lean Six Sigma model applied to PAT.

Given the lack of information from the original development work, a characterization study was initiated to evaluate the impact of lubricant concentration, mixing time, and whether the intensifier arm was used. The ICH Q8 guidance describes this evaluation as defining the knowledge space for the process. An orthogonal experimental design, using a blocked design for the intensifier bar, was performed. Mean granulation size and PSD and lubricant PSD data were measured and kept constant for the study. The results indicated that lubricant concentration and mixing time KPIVs were both significant at all three dissolution points. The intensifier bar did not have an effect. Key KPOVs measured were drug dissolution, drug content uniformity, and tablet appearance.

Define

ICH Q8 discusses identifying the optimum design space for the process. The design space is a subset of the overall knowledge space for the manufacturing process. A graphical representation of the relationship between the knowledge, design, and control space is shown in Figure 5. In evaluating the influence of key process inputs, the team focused upon a tiered approach to reducing PAT risk. It was agreed the minimum acceptance criteria was to achieve drug content uniformity. Once the control space was established, the

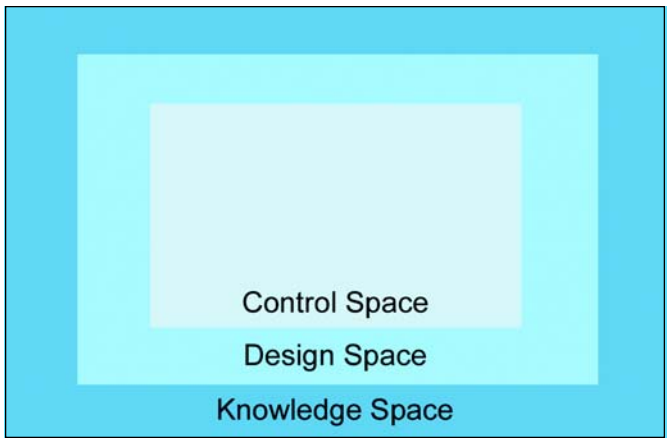


Figure 5. Relationship of knowledge, design, and control spaces.

behavior of the lubricant would be evaluated. The objective was to find a control space in which drug content and lubricant uniformity could be assured.

The knowledge space defines the boundaries within which the process inputs or KPIVs can be varied. However, within the knowledge space, some parameters at their limits may not produce acceptable product and some parameters may have no impact on the critical KPOVs (in this case study - content uniformity, dissolution, and lubricant content). The design space then represents the widest range of each of the KPIVs within which acceptable product meeting all of the KPOV specifications can be manufactured under ideal and controlled conditions. The control space represents a further tightening of the design space of the KPIVs in which acceptable product is assured of meeting specifications, allowing for process drift and measurement and sampling uncertainty.

The PAT team initiated a follow-on study, designed to characterize the design space. The lubricant concentration was fixed at 1.5%, and the intensifier bar was not used. In order to evaluate the impact of granulation PSD, the percentage fines was evaluated. Two different suppliers of lubricant also were evaluated. All satisfied the revised specification for the lubricant. The DOE evaluated the following possible input parameters:

1. Mixing time: 7 to 12 minutes
2. Granulation Percent Fines: 10 to 40%
3. Lubricant Lots: 1 to 2

The study revealed that mixing time and granulation PSD were significant KPIVs for drug dissolution at the two, four and eight hour time points. The lubricant lots were not significant contributors to either drug content uniformity or lubricant content uniformity. All lots passed Level 1 dissolution testing.

Optimize

The next step in identifying the final processing space is to identify the control space. The control space represents a range of critical parameters within which the process will yield an assured output within the KPOV specifications allowing for sources of statistical uncertainty. It also represents the basis for the control architecture to be adapted for the PAT solution. Powder mixing theory states that the components that impact blend uniformity are: granulation/blend physical characteristics, including particle size distribution, shape and moisture content, powder bulk density, and Van Der Waals forces. Of these, granulation particle size is the most significant factor. Given that granulation PSD was identified as a significant contributor, a Six Sigma exercise was initiated to understand the variability in the final granulation. Milling steps upstream of the blend step were evaluated and modifications to the milling set-up to control the feed rate of granulation were made. A screening study was repeated to determine if the new granulation PSD was still a significant contributor to blend uniformity and it did not come up as significant at the 95% confidence interval. Based upon this, the control strategy established a baseline of lubricant distribution to serve as the comparability criteria for the PAT solution downstream. The team did not focus on the drug content uniformity since the knowledge and design space studies had moved the process away form the edge of failure, while characterizing the variability around the KPIVs that would affect drug content uniformity.

Measure

The challenge in developing an in-line metric for ensuring proper mixing of the lubricant was the lack of an off-line test currently being performed for lubricant content in tablets. A baseline examination of tablets manufactured during the control phase was performed using Mass Spectroscopy (MS) in order to understand the variability around the control space. Tablets which exhibited poor dissolution also were evaluated from the original failed lots. The results of the MS data are shown in Table A. The most striking observation is that the tablets which exhibited poor dissolution had significantly higher levels of lubricant.

Automate

The team had sufficient understanding of the behavior of the current process, its KPIVs and KPOVs, to move to identifying an automation solution. The PAT team included an external automation firm with a strong understanding of process, Design for Six Sigma, and GAMP 4[8] to complement their experience in custom automation. This is a significant consideration given the intimate relationship between the technical solution and quality and regulatory considerations for the project. Having a solutions provider that possesses the systems to integrate the requirements of Quality by Design (QbD) is a major advantage in developing the scientific argument that the in-line solution is an equivalent or superior surrogate to the off-line analytical solution and in generating the necessary documentation trail to support subsequent validation.

The team approached the automation solution in phases. The first phase was designed to ensure there was a solid understanding of the existing process performance using off-line analytical tools. Tablet performance was currently mea-

sured using HPLC for content uniformity and potency assessment. Tablet dissolution coupled with UV spectroscopy determined the tablet's release profile. Currently no off-line assessment was performed on the lubricant. This had been found to be a key factor in achieving the desired tablet dissolution profile. The second phase was to establish a correlation with the new surrogate analytical method. The last phase was to demonstrate that the hardware solution and control algorithm resulted in tablets that satisfied the product's release criteria. The team focused on establishing a correlation between an off-line and in-line method for lubricant concentration. Tablets were analyzed using MS and FT-NIR to establish the correlation. The results are shown in Table B. Based on the results of the correlation study, the team demonstrated that the in-line solution was viable and they could proceed with developing an in-line solution.

Verify

The verify step is used to establish a basic proof of concept that the principles of the solution are viable. In the previous phase, the team attempted to establish a correlation between the offline and in-line measurement systems. Adherence to the Six Sigma methodology had narrowed the control space to keep the process sufficiently far from the edge of failure. The first focus was establishing a measurement for the lubricant in the blending step, which could be used to dictate the blending time. It is important to note we are not concerned with lubricant weighing errors; rather with the distribution of lubricant throughout the granulation. Lubricant integration with the granulation particle has been shown to impact the dissolution of some controlled-release tablets as mixing time increased.

Since confidence was high that material mixed for seven to 12 minutes resulted in tablets with acceptable dissolution, then the correlation with lubricant concentration could be one trigger used to prevent overmixing. A non-destructive test was required to demonstrate comparability. A sample size of 100 tablets was selected. With the selection of FT-NIR as the measurement tool, a blender was modified with a self-contained analytical probe and analyzer and equipped with a wireless transmission system to deploy as a proof of concept system. The final control space screening study was repeated. Measurements were taken from the in-line sensor and tablets were tested using MS for lubricant content. In addition, tablets were tested for content uniformity, potency, and dissolution at the three, four, and eight hour time points.
One of the key metrics for process performance is a measure of process capability, Cpk. This metric for a process with a normal (or close to normal) distribution and a two-sided specification is described by the equation:

$$Cpk = \min\left[\frac{USL - \bar{x}}{3s}, \frac{\bar{x} - LSL}{3s}\right]$$

Where, USL/LSL = Upper/Lower Spec Limit
X = Mean
S = Standard Deviation (sigma)

Cpk assumes that the process is in statistical control. In simple terms, Cpk compares the spread of your process to the spread of your specification and how close the mean of that

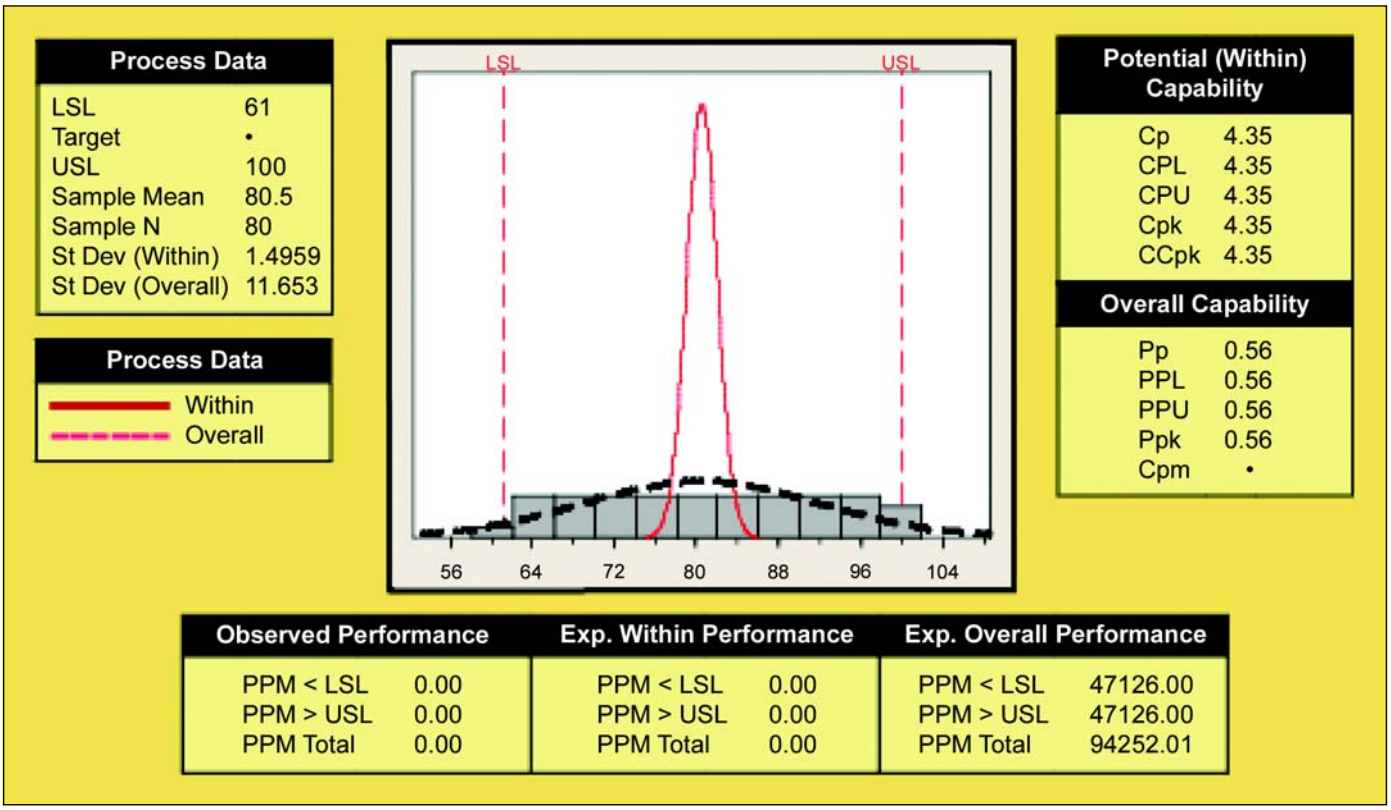


Figure 6. Process capability curve for eight hour tablet dissolution time point.

Tablet	MS% Lubricant	T-NIR% Lubricant	Comment
Lot A	1.62	1.43	Control Space Lot
Lot B	1.76	1.68	Control Space Lot
Lot C	1.53	1.37	Control Space Lot
Lot D	1.67	1.59	Control Space Lot
Lot E	1.48	1.44	Control Space Lot
Lot F	1.51	1.49	Control Space Lot
Lot G	1.39	1.21	Control Space Lot
Lot H	1.71	1.47	Control Space Lot
Failed Lot 1	5.12	4.46	Failed L1 Dissolution
Failed Lot 2	6.11	4.87	Failed L2 Dissolution
Failed Lot 3	3.98	3.12	Failed L1 Dissolution
Failed Lot 4	5.45	4.61	Failed L2 Dissolution

Table B. Analytical method comparison.

process is to the specification limits. A high number (>1.33) indicates that the probability of getting an out-of-spec product is very small. Cpk was calculated after determining that the process was in control through a control chart. All dissolution time points had a process capability greater than 1.33 (4 sigma process). The process capability chart for the eight hour time point is shown in Figure 6.

The results illustrate that the FT-NIR system was capable of controlling the process and delivering compliant product. Based upon these studies, a change control notice was initiated and the production equipment was modified.

Validate

The final step in the process was to validate the equipment and process. The Six Sigma process dictated the elements to be completed as follows:

1. Generate the Final Development Report
2. Baseline the Equipment
3. Modify Operational SOP
4. Modify Maintenance SOP
5. Modify Calibration Program
6. Software Validation-Part 11 Compliance
7. IQ/OQ/PQ
8. MS and FT-NIR Method Validation
9. Regulatory Update

Conclusion

The statistical tools and toll-gate process of Six Sigma provides a best practice process for characterizing, controlling, and reducing process variation that is necessary to successfully deploy PAT. The partnership of Six Sigma and PAT was intended to characterize and implement a control and measurement solution, which would minimize the likelihood of a controlled-release tablet failing dissolution. The team used a modified DCOV model subdivided into eight phases designed to ensure that the basic requirements of the ICH Q8 requirement for QbD were satisfied. This framework ensured all aspects of the project were addressed in an efficient and methodical manner with the scientific rigor necessary to implement an in-line control architecture integrated throughout the process.

References

1. Maes, I. and B. Van Liedekerke, "The Need for a Broader Perspective if Process Analytical Technology Implementation is to be Successful in the Pharmaceutical Sector," *Journal of Pharmaceutical Innovation,* Volume1, Number 1, September/October 2006, pp. 19-21.
2. Kourti, T., PhD, "Process Analytical Technology and Multivariate Statistical Process Control: Wellness Index of Product and Process – Part 1," *PAT Journal,* Volume 1, Issue 1, September/October 2004, pp. 13-19.
3. Kourti, T., PhD, "Process Analytical Technology and Multivariate Statistical Process Control: Wellness Index of Product and Process – Part 2," *PAT Journal,* Volume 2, Issue 1, January/February 2005, pp. 24-29.
4. Kourti, T., PhD, "Process Analytical Technology and Multivariate Statistical Process Control: Wellness Index of Product and Process – Part 3," *PAT Journal,* Volume 3, Issue 3, May/June 2006, pp. 18-24.
5. Harry, Mikel and R. Schroeder, Six Sigma: The Breakthrough Management Strategy Revolutionizing the World's Top Corporation, Doubleday, 2000.
6. Pyzdek, T., The Six Sigma Handbook: A Complete Guide for Green Belts, Black Belts and Managers at All Levels, Revised and Expanded, McGraw-Hill, 2003.
7. Brue, G., Design for Six Sigma, McGraw-Hill, 2003
8. *GAMP 4: The Good Automated Manufacturing Practice Guide for the Validation of Automated Systems*, International Society for Pharmaceutical Engineering (ISPE), Version 4, December 2001.

About the Authors

Bikash Chatterjee is President of Pharmatech Associates, Inc. He has been involved in the bio-pharmaceutical, pharmaceutical, medical device, and diagnostics industry for more than 20 years. Most recently, he served as the vice president, Pharmaceutical Operations for Aradigm Corporation where he was responsible for establishing their process development, engineering, validation, facilities, and manufacturing capabilities. Prior to joining Aradigm, Chatterjee was the plant manager responsible for manufacturing Boehringer- Mannheim's disposable coagulation testing system. Chatterjee has designed, built, and qualified multiple facilities throughout his career, ranging from centralized warehousing to large capacity BSL-2 manufacturing facilities. His expertise includes site selection, project management, and design and validation of facilities for both US and European regulatory requirements, and he has been involved in the design and validation of biopharmaceutical facilities in the US, Europe, and Asia. From 1988 to 1992, he held a number of senior manufacturing positions at various

pharmaceutical companies, including Syntex Corporation. Chatterjee is a certified ISO 9000 Lead Assessor, a Six Sigma Master Black Belt, and has more than 15 years of experience in the implementation of Lean Manufacturing programs in the life sciences industry. He holds a BA in biochemistry and a BS in chemical engineering from the University of California at San Diego. He can be reached by telephone at: +1-510-760-2456 or by e-mail at: bchatterjee@pharmatechassociates.com.

Dr. Jeremy D. Green is a Senior Consultant for Pharmatech Associates. He is a Certified Lean Six Sigma Master Black Belt, American Society for Quality Certified Six Sigma Black Belt, and Certified Quality Engineer with 20 years of experience in quality and manufacturing management. His background includes work in the pharmaceutical process automation, food, semi-conductor, and electronics industries. Dr. Green received his PhD from Indiana State University and his BA from the University of Illinois. He can be reached by telephone at: +1-541-754-9164 or by e-mail at: jeremygreen7@comcast.net.

Pharmatech Associates – SIPR, 1098 Foster City Blvd., Suite 303, Foster City, California 94404.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Lean Data Analysis: Simplifying the Analysis and Presentation of Data for Manufacturing Process Improvement

by Malcolm Moore

This article introduces a data analysis maturity model that maps various tools and methodologies aimed at predicting, analyzing, improving, or controlling the drivers of product quality to the extent to which these techniques may help reduce defects. By mapping tools currently deployed in a particular manufacturing facility to the maturity model, it is possible to define a cost-effective road map for various initiatives aimed at improving product quality through increased process understanding. Pragmatic data analysis and reporting approaches are introduced to aid process understanding for mainstream users and the deployment of that understanding in manufacturing to increase product performance.

Introduction

To achieve increased process understanding via Six Sigma, Process Analytical Technology (PAT), or other methodologies requires adoption of at least three types of technology:

1. measurement technology to gauge process and material inputs and intermediate product
2. data integration and cleansing technology to bring together disparate sources of data – including process, material, intermediate, and final product data sources – in a timely and effective manner
3. data analysis and reporting technology to bring understanding from integrated data collected in the context of a problem or improvement opportunity

Emphasis on measurement technology alone will increase the extent to which process and materials are measured, and will drive up costs and data volumes. The lack of effective data integration and data analysis methods for all consumers of the data will limit the growth in process understanding and the ability of manufacturing to exploit this understanding.

Figure 1 presents a high-level process model of data integration and data analysis in manufacturing. The components represented in blue depict the IT function of integrating disparate data sources, including databases, electronic and paper sources, then cleansing and transforming data to an analysis-ready state with a data model that is easily maintained and extended as the number and type of data sources grow.

The need for a data integration solution – and the level of sophistication required of it – will depend upon the extent to which inputs are measured. In newer production lines, it may be common to measure hundreds of input variables via NIR spectroscopy, and other inline,

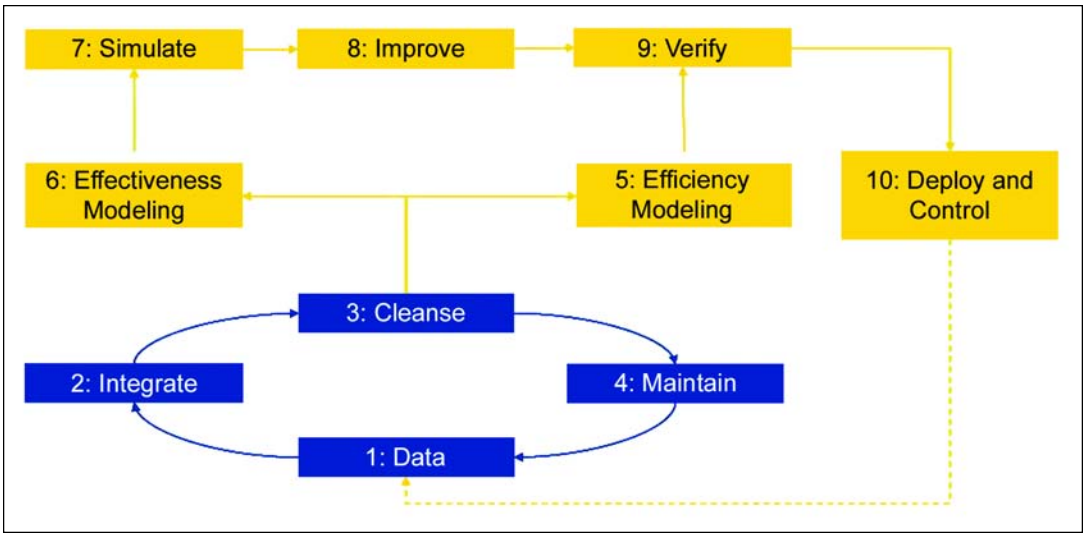


Figure 1. PAT Data Integration, Modeling, Improvement, and Control Process.

at-line, online, or offline methods, requiring a data integration solution. However, older production facilities may focus on offline laboratory testing of intermediate and end-of-line products and use measurement technologies for process inputs on an as-needed basis.

The process steps represented in orange symbolize some ways that business users might analyze their data. At least two different approaches to modeling the relationships in cleansed or analysis ready data are available and the terms *efficiency* and *effectiveness* modeling are introduced to distinguish the two approaches. Efficiency modeling is used to classify models that use multivariate relationships to predict manufacturing problems. Such models do not necessarily result in model simplification or reduction of the number of dimensions that need to be measured, nor do they greatly increase understanding of how the key inputs drive variation in product quality. Effectiveness modeling, on the other hand, is used to describe approaches that identify the critical few inputs and define empirical transfer functions that describe how these key inputs operate together to drive manufacturing problems or issues, increasing our understanding of how those inputs affect variations in quality. These two modeling approaches are described in more detail below and are illustrated by case studies.

This article focuses on pragmatic approaches to data analysis and reporting that work regardless of the extent to which inputs are measured. It introduces ways of simplifying data analysis and reporting approaches associated with PAT, Six Sigma, and related methodologies and proposes a way to define a road map for the adoption of manufacturing improvement technologies relative to the current level of measurement maturity. Mapping of a broad set of tools to a data analysis maturity model are presented along with examples of various data analysis approaches, including a set of pragmatic analysis techniques that are simple to apply and understand at all levels of an organization.

PAT Data Analysis Methods

Modeling Approaches

Statistical modeling approaches to PAT are classified in two ways: models for increasing the efficiency of manufacturing – reducing waste; and models for increasing effectiveness of manufacturing – enhancing process understanding and utilizing it to improve manufacturing performance.

Efficiency models consist of classification modeling techniques, such as discriminant analysis, cluster analysis, and decision trees, along with predictive modeling techniques such as Partial Least Squares (PLS) and Principal Component Regression (PCR). These techniques exploit the multivariate relationships among a large number of measured inputs to predict product performance or batch failures ahead of time. Compared with effectiveness modeling methods,

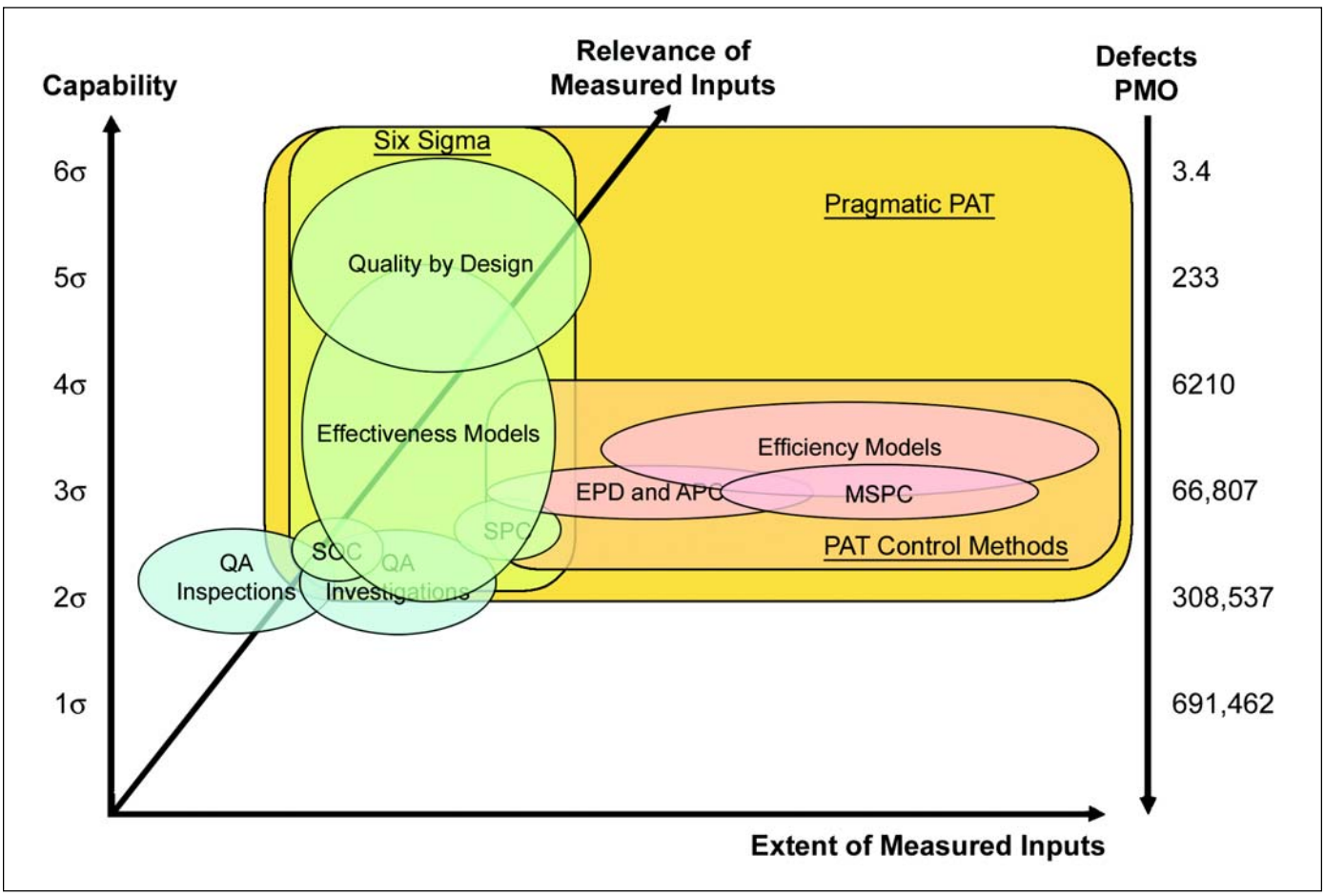


Figure 2. Mapping of data analysis technology to process capability and dependence on extent and relevance of measured inputs.

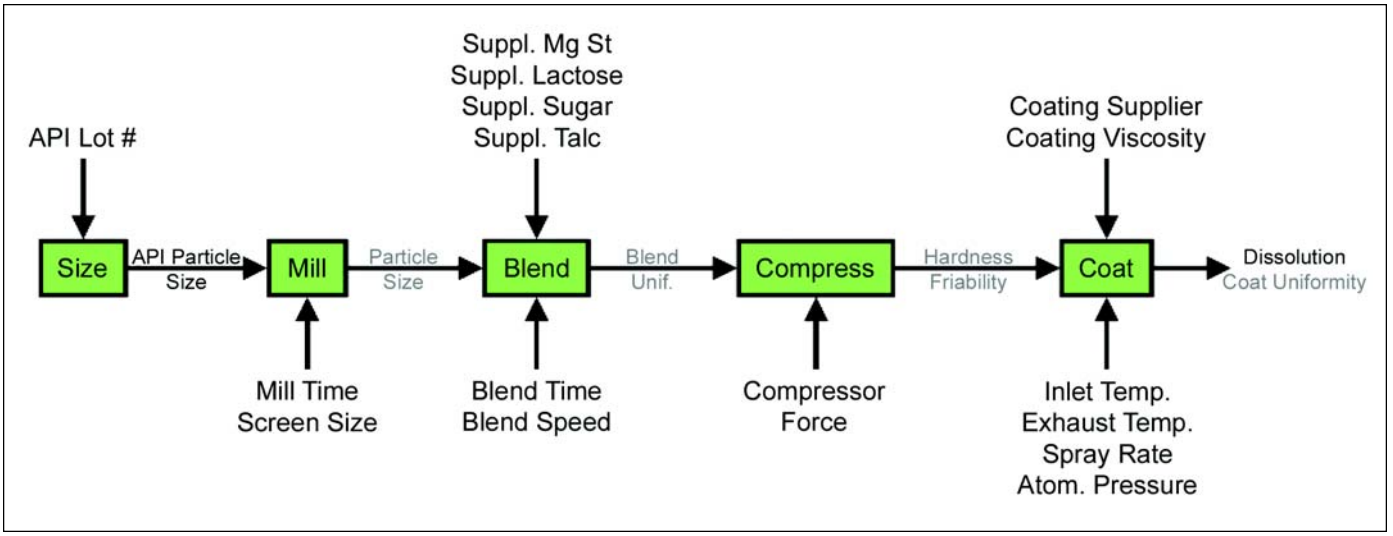


Figure 3. Key processes and inputs associated with excessive variation in 60 minute dissolution.

efficiency models require a large number of measured inputs – in fact, the more the better – and tend to be used for "black box" batch classification or prediction of likely product performance. In other words, they make good predictions, but they do not necessarily deliver fundamental changes in process understanding.

Effectiveness models consist of variable reduction or exploratory data analysis methods, such as data mining, correlation analysis, process mapping, cause-and-effect analysis, Quality Function Deployment (QFD), Failure Mode Effects Analysis (FMEA) to identify the critical few inputs that are investigated in more detail via Design of Experiments (DOE), multiple regression, and generalizations of multiple regression for non-normally distributed measures of product quality. With care, these latter techniques develop empirical models that approximate the causal relationships between the critical few inputs and product quality.

Examples of some of these different modeling approaches are provided in the case studies below.

		Actual			
	Count Total % Col % Row %	Too Low	Good	Too High	
Predicted	Too Low	1 1.39 100.00 50.00	1 1.39 1.54 50.00	0 0.00 0.00 0.00	2 2.78
	Good	0 0.00 0.00 0.00	63 87.50 96.92 98.44	1 1.39 16.67 1.56	64 88.89
	Too High	0 0.00 0.00 0.00	1 1.39 1.54 16.67	5 6.94 83.33 83.33	6 8.33
	Total	1 1.39	65 90.28	6 8.33	72

Table A. Predicted by actual batch classification.

Maturity Model

Figure 2 may be useful when considering the best mix of data analysis methodologies to increase process understanding for a particular manufacturing facility. It may help establish a baseline for your manufacturing facility with regard to product quality performance, define goals for a proposed PAT investment, and help define a road map for getting to those performance goals.

This maturity model maps data analysis methodologies against sigma capability. Sigma is the measure of variability in the product quality measure, usually calculated by assuming the product quality measure is normally distributed. A 2 sigma process is one where the mean ± two standard deviations coincide with the specification limits of the product quality measure. In this case, approximately 5% of batches would not meet the required quality specification (approximately 2.5% in each tail of the distribution). Defects Per Million Opportunities (PMO) is calculated after assuming a shift of 1.5 sigma in the mean of the product quality measure. Hence, a 2 sigma process encountering a 1.5 sigma shift in the mean from target would result in 308,537 defects PMO. Thus, a high sigma capability value such as 5 or 6 is required to ensure little or no defects after allowing for a shift in the process mean.

Most mature manufacturing facilities deploy a combination of QA inspections, Statistical Quality Control (SQC) – control charts applied to product quality measures, and QA investigations in an attempt to trace the cause of batch exceptions. Such approaches generally achieve sigma capability of up to 2.5. The introduction of SPC, where control charts are applied to intermediate product measurements, may get performance up to the region 3 sigma.

More sophisticated control methods, such as End-Point Detection (EPD) and Advanced Process Control (APC) can be deployed to reduce variation in intermediate product and help reduce variation in final product to 3 sigma or thereabouts. Utilization of inline measurement tools in conjunction with EPD to achieve a specified moisture content in

drying operations or specified blend uniformity in blending operations, or APC to have short loop controls to make "corrective" adjustments during unit process operations are appealing control strategies. However, to have real impact, these approaches require detailed understanding of the extent to which changes to the mean, within-batch and between-batch variability of factors, such as moisture content, affect the sigma capability of final product quality. Used in isolation, EPD and APC are unlikely to get final product capability much beyond 3 sigma. Multivariate Statistical Process Control (MSPC) is an extension of SPC that exploits the correlations between measured inputs to give greater resolution in detecting problems ahead of time and reduce the extent of false alarms. Like EPD and APC, MSPC is most effective when deployed in conjunction with effectiveness modeling strategies. Early indications of process drift, detected by a control mechanism when investigated via effectiveness modeling methods, may result in increased process understanding that may be used to revise the control strategy to sustain the gain. Used in isolation, neither MSPC nor any other control method is likely to get final product quality appreciably beyond 3 sigma capability.

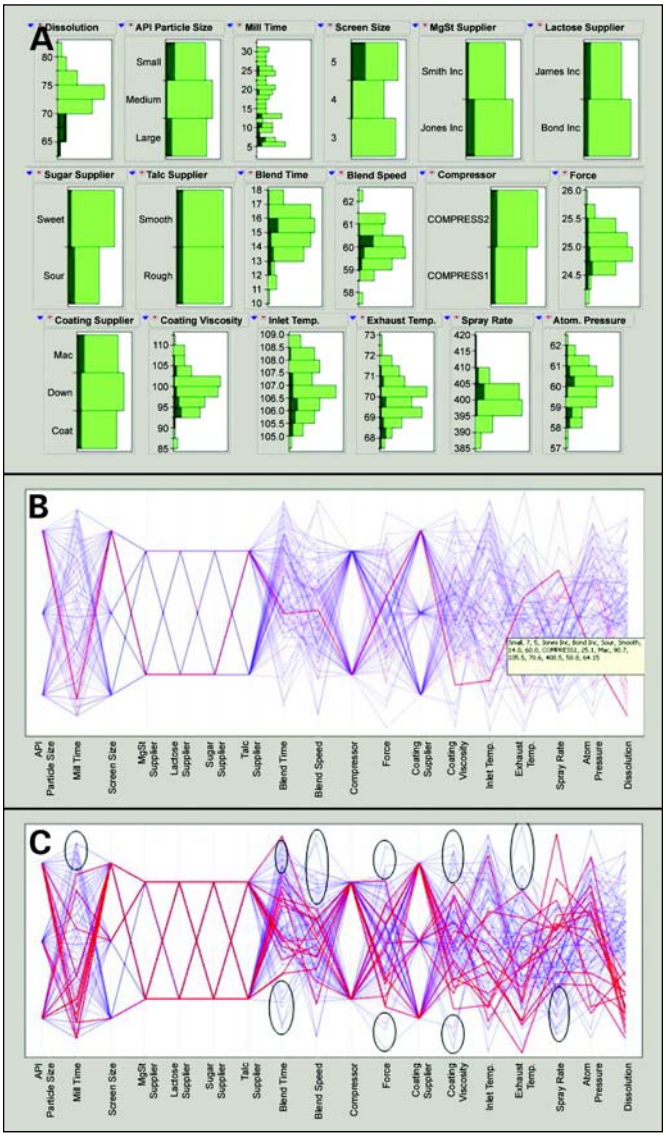


Figure 4. Visual exploration of relationships.
a. Distributions of 60 minute dissolution and key inputs with dissolution failures identified in dark green.
b. Parallel of key inputs with the values of the processing conditions identified for a failing lot.
c. Parallel plot with settings of some key inputs worthy of further investigation.

Efficiency models such as PLS and PCR work best when tens or hundreds of measured inputs are available for each production batch. They exploit the correlations between the inputs to produce reliable classification or prediction models of product quality. These techniques need to be used in conjunction with effectiveness modeling methods if the goal is to increase sigma capability of product quality through increased process understanding. Efficiency models provide an effective basis for prioritizing the input variables for inclusion in effectiveness modeling activities. Used in isolation, efficiency models are likely to get capability in the region of 3 to 4 sigma.

The focus of effectiveness modeling is to identify the critical few inputs and to develop empirical models of the effects of these on product quality that approximate the causal relationships between inputs and product quality. This new knowledge is then deployed to reduce variation in final product quality and achieve performance requirements through revised process and material specifications and controls. Effectiveness modeling approaches applied to the process development of new products is otherwise called Quality by Design (QbD). For new products, Quality by Design is a good way of achieving six sigma quality performance. This approach ensures a high level of process understanding along with cost-effective control strategies in manufacturing that are based on measurement and control of the critical few relevant inputs. Measuring and controlling everything that can be measured increases production costs and cycle times unnecessarily. Compared to process development of new products in R&D, effectiveness modeling of mature manufacturing processes requires a little more care due to the inherent correlations in measured inputs and the limited range over which inputs are varied. With appropriate consideration of these constraints, effectiveness modeling can deliver increased process understanding and higher levels of sigma capability, along with specifications and controls concerning the relevant few process and material inputs.

Efficiency modeling along with advanced control strategies, such as EPD, APC, and MSPC, are classified as PAT Control Methods. Effectiveness modeling and QbD are classified as Six Sigma Methods. Lean Data Analysis or Pragmatic PAT as illustrated in the case studies is an appropriate blend of simplified Six Sigma Methods and PAT Control Methods. The best blend for a particular manufacturing facility depends on where the facility is positioned within the matrix.

Various factors need to be considered when determining the best mix of data analysis methodologies to enable increased process understanding for a particular manufactur-

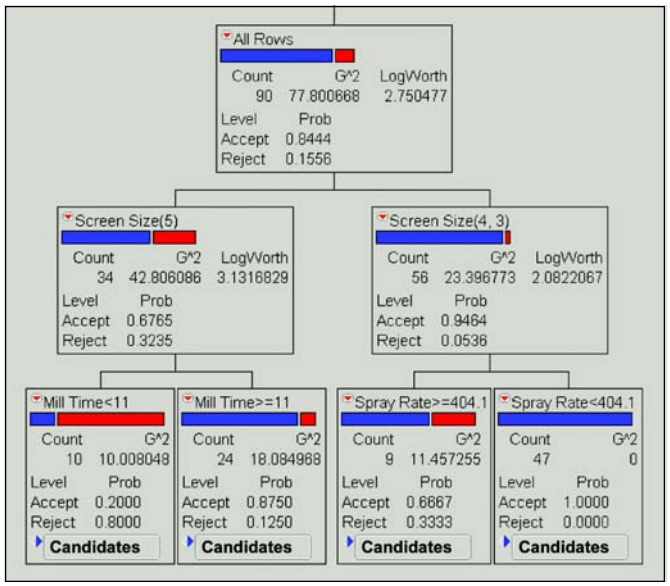


Figure 5. Recursive partitioning decision tree.

ing facility, including product maturity, sigma capability, and the extent and relevance of measured and unmeasured inputs. A mature manufacturing facility is unlikely to have extensive inline, at-line, or online measurement tools in place; therefore, greater emphasis on effectiveness modeling and Six Sigma approaches will be appropriate. For newer manufacturing processes with an extensive number of measured inputs, there may be a greater mix of PAT Control Methods although appropriate use of effectiveness modeling methods also will be required to ensure fundamental understanding of the process. After positioning a particular manufacturing facility within the maturity matrix, it is possible to map out short- and long-term goals of a quality improvement or PAT investment and define a high-level road map for achieving those goals.

Case Studies

These are fictional case studies based on simulated data, copies of which are available on request from the author. The scenarios around which the data have been simulated are fairly typical of the data sparse situation of mature manufacturing and data rich position of some manufacturing facilities of new products. These simulated situations are not based on any particular case, but they do try to reflect the realities of the two situations and by so doing provide data analysis examples that are easier to apply and understand for the mainstream.

Case Study 1: Mature Manufacturing with Few Measured Inputs

This case study concerns a manufacturing facility that has been producing an established product in the form of solid doses at various concentrations for several years. Current measurement systems are based on storing finished material, while offline QA tests are performed to assure the finished product meets the performance specification.

The case study focuses on investigating the process for tablets produced at a single concentration. The key performance metric is 60-minute mean dissolution, which must be no less than 70%. Historically, 16% of production batches fail to meet the 60-minute dissolution requirement and QA investigations into these lot failures rarely find an assignable cause.

In this data-sparse scenario, the manufacturing team was commissioned to investigate the process and dramatically improve sigma capability. The team adopted a variety of effectiveness modeling techniques, starting with process mapping, which was used to identify the key process steps and to identify the set of inputs that were most relevant to the problem and easy to collect information about retrospectively. The results of this process-mapping exercise are documented in Figure 3; the set of inputs that might have an impact on 60-minute mean dissolution and are easily collected retrospectively are identified in black type. Inputs occurring above a process step represent material properties; inputs occurring below a process step represent process parameters.

Data on the inputs identified in black type along with mean dissolution were collated for the last two years of production batches, which resulted in a data set consisting of 90 rows and 19 columns.

Exploratory data mining methods as indicated in Figure 4 were deployed to help determine the inputs most strongly associated with dissolution failures. Part (a) of Figure 4 shows simple histograms of each variable with the failing batches identified in dark green. This shows a particularly strong relationship between screen size in the milling step and batch failure with a larger screen size resulting in a greater proportion of failures – presumably a larger screen size results in larger API particle size and these larger particles take longer to dissolve. Spray rate in the coating

V9	V15	V18	V21	% at stage 3-4
0.25	0.5	0.9	0.7	29.24
0.25	0.35	0.9	0.95	27.10
0.25	0.5	0.65	0.95	17.88
0.25	0.2	0.65	1.2	21.93
0.2	0.2	0.9	0.7	33.24
0.3	0.2	0.4	0.95	22.47
0.2	0.2	0.4	1.2	19.46
0.3	0.2	0.9	0.7	34.69
0.3	0.5	0.9	1.2	17.83
0.2	0.5	0.9	1.2	14.61
0.3	0.35	0.65	0.7	25.96
0.25	0.2	0.4	0.7	23.77
0.3	0.5	0.4	0.7	20.36
0.2	0.5	0.4	0.7	19.52
0.25	0.35	0.4	1.2	14.80
0.2	0.35	0.65	0.95	20.56

Table B. DOE worksheet.

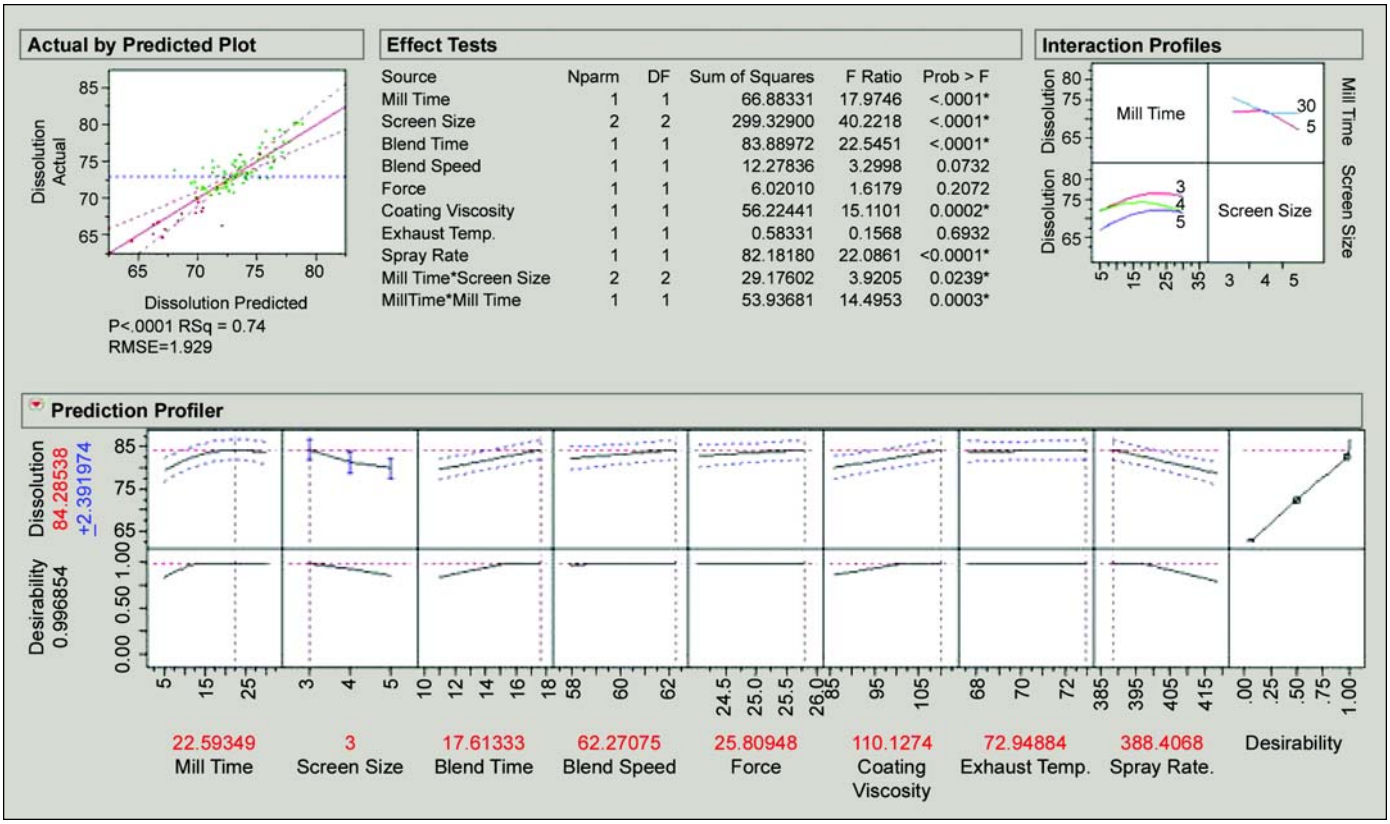


Figure 6. Multiple regression analysis summary.

step also has a strong association with batch failures; in particular, lower spray rates have no batch failures. Part (b) of Figure 4 shows the multivariate relationship of the 18 variables in a single graph called a parallel coordinates plot. There are 90 lines on this graph – one line for each production batch – with the path of each line representing the processing conditions of each batch along with the resulting dissolution test result for that batch. By design, there is no scale on the y-axis; instead, a plotting range for each variable is selected to show the span of data values for that variable. The failing batches are identified in red and the passing batches in blue. The values of each variable for one of the failing batches is illustrated in bold red, showing API with a small particle size, processed with a mill time of seven minutes, screen size of five, and so on. Part (c) of Figure 4 shows the parallel coordinates plot with all failing batches identified in bold red; this version of the graph enables the identification of processing conditions associated with passing or failing batches. Some processing conditions associated with passing batches are circled, e.g., high mill time, low and high blend time (with one exception), high blend speed, low and high force, low and high coating viscosity, high exhaust temperature, and low spray rate appear to be more favorable processing conditions. Potential interactive effects of two or more inputs on dissolution can be investigated on both graph types by coloring the points according to different rules. For example, to investigate the size of the interactive effect of blend time and blend speed on mean dissolution, a cut point would be defined for each input (giving high and low values of each input) and then color the points differently for the four combinations. We would then look to see if there is an appreciable change in mean dissolution across the four combinations of the two variables. One potential draw-back of the parallel coordinates plot is that it is not as effective at exploring the effects of categorical variables such as API Particle Size, Screen Size, and Coating Supplier, due to the inability to display the proportion of failing/passing batches processed at each level of a categorical variable. Nonetheless, it is a good visual data mining tool that helps identify key continuous variables for further investigation.

Another useful exploratory data mining method is recursive partitioning. This method repeatedly partitions data according to a relationship between the input variables and an output variable, creating a tree of partitions. It finds the critical input variables and a set of cuts or groupings of each that best predict the variation in batch failures. Variations of this technique are many and include: decision trees, CART™, CHAID™, C4.5, C5, and others.

Figure 5 shows the resulting decision tree using recursive partitioning to explore the main drivers of batch failures. The right-hand branch of the decision tree shows that 47 of the 90 batches were processed using a screen size of four or three in conjunction with a spray rate less than 404. All 47 batches passed the dissolution test. At the other extreme, the left-hand branch shows that 10 batches were processed using a screen size of five and a mill time of less than 11. Eight of these batches failed the dissolution test.

These exploratory data mining methods have collectively

identified a subset of inputs – Mill Time, Screen Size, Blend Time, Blend Speed, Force, Coating Viscosity, Exhaust Temperature, and Spray Rate – worthy of further investigation. The methods have several advantages over conventional statistical approaches, including:

1. ease interpretation and communication, enabling everyone to gain insight into the potential key relationships in data

2. inform the mainstream about the principles of statistical thinking, particularly those of modeling variation in process outputs and identifying the key drivers of process variation

The effects of this subset of input variables upon 60 minute mean dissolution were investigated in more detail using multiple regression in Figure 6. The graph at the top shows that the model predicts actual values of dissolution reasonably well, and the effects tests summary shows that all, but blend speed, force, and exhaust temperature significantly contribute to variation in 60 minute mean dissolution at the 5% level. Further mill time and screen size have an interactive effect and mill time has a quadratic effect on 60 minute mean dissolution as illustrated in the interaction profile. The prediction profiler at the bottom of Figure 6 shows the direction and strength of the effects of each factor on 60 minute mean dissolution with the optimum settings of each input given in red. Since blend speed, force, and exhaust temperature do not significantly affect 60 minute mean dissolution at the 5% level, any value of these three inputs within the observed range are acceptable. The anomaly of one failing batch with a high blend time in Figure 4(c) was due to a low mill time (10 minutes) and screen size of five.

To investigate process robustness against the proposed new set points, the simulation illustrated in Figure 7 was performed. Using the multiple regression model as the transfer function between the key process inputs and 60 minute mean dissolution, 1000 simulations were performed with mean settings close to the best setting of the inputs with tolerances as indicated in Figure 7. The target and tolerance used for blend speed, force, and exhaust temperature was the same as currently used in manufacturing since 60 minute mean dissolution was robust to this level of variation in these three inputs. The target and tolerance of mill time, screen size, blend time, coating viscosity, and spray rate were adjusted per the knowledge gained via multiple regression to ensure acceptable distribution of 60 minute mean dissolution relative to the lower specification limit of 70%. The simulation confirms expectations of consistent product performance with a predicted Cpk of 1.4 (equivalent to a sigma level of 5.6). The proposed solution is wholly within the bounds of the currently validated process.

Case Study 2: New Production Facility with Many Measured Inputs

This case study concerns a relatively new manufacturing facility that has been producing commercial batches of an inhaler product for a couple of years. Extensive inline measurement systems were designed into the facility, resulting in a data-rich environment of 520 measured inputs. The first 30 inputs are processing parameters of the milling, blending, and packaging steps; variables 31-100 are properties of ingredient 1; variables 101 to 170 are properties of ingredient 2; and the remaining variables are properties of ingredient 3 (active ingredient).

The key performance metric is a percentage of a given dose reaching stage 3-4 of a cascade impactor, which must be between 15% and 25%. Since the start of commercial production, 240 batches have been manufactured, approximately

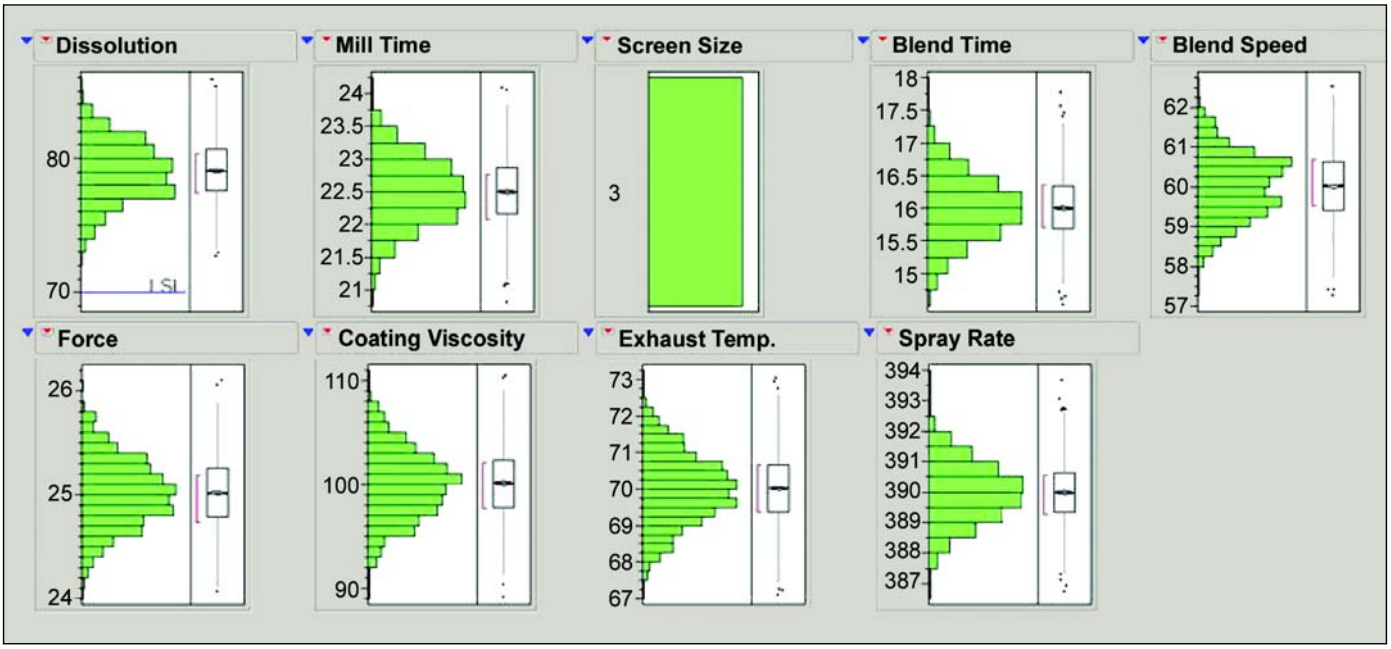


Figure 7. Simulation study to investigate process robustness.

14% of which have failed to meet the performance requirement of the cascade impactor test. QA investigations into these batch failures have been unable to identify any obvious assignable causes.

In this data-rich scenario, the manufacturing team commissioned with investigating the process and dramatically improving sigma capability adopted a variety of effectiveness and efficiency modeling techniques. Figure 8 illustrates the results of recursive partitioning to help determine the inputs most strongly associated with the percentage of a dose reaching stage 3-4.

The decision tree shows how the distribution of % at stage

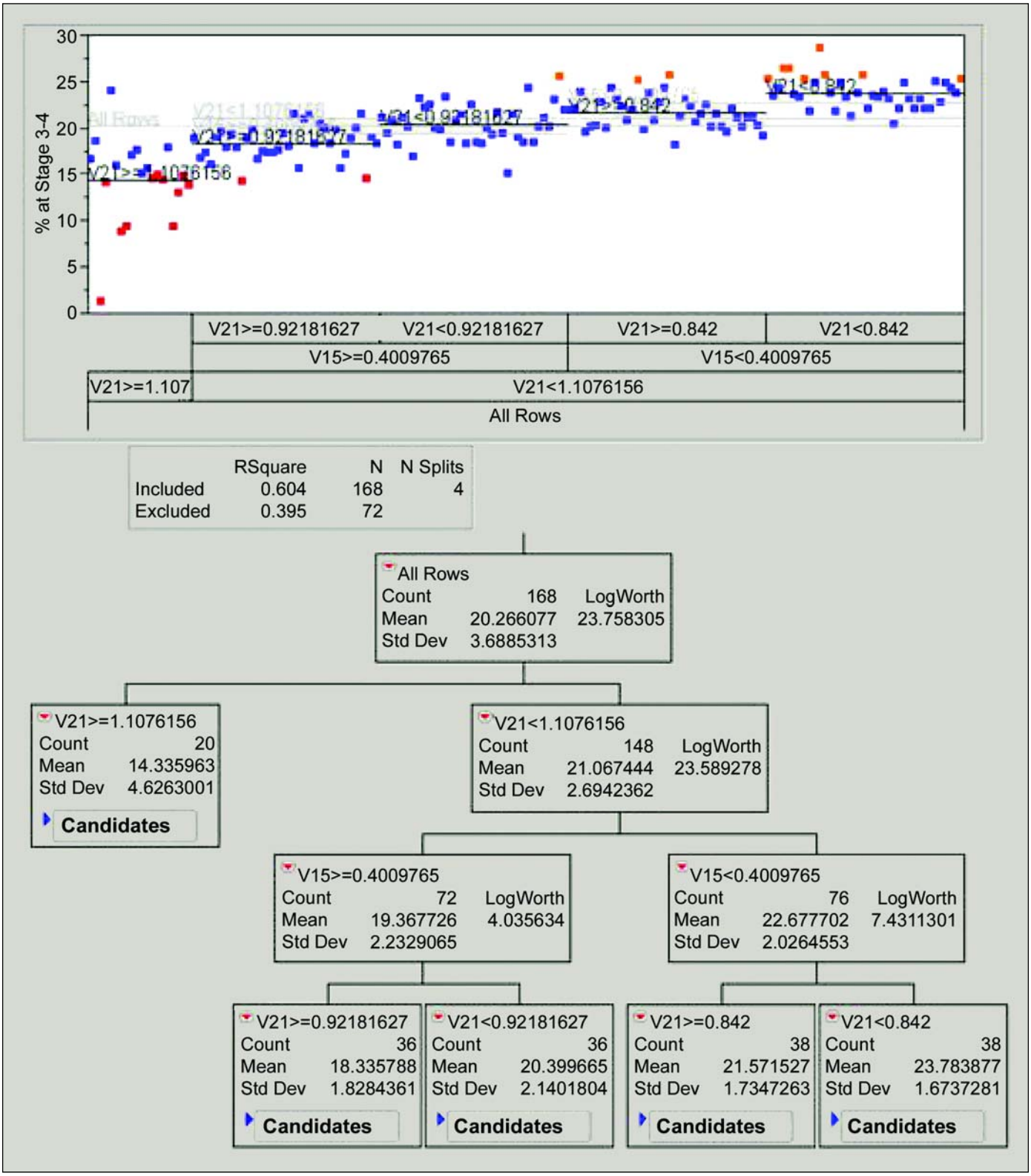


Figure 8. Recursive partitioning decision tree identifies inputs most strongly associated with variation in % at stage 3-4.

3-4 changes according to splits derived from the levels of two process variables - V21 and V15. The left-hand branch of the decision tree shows that when V21 >= 1.1, the distribution of % at stage 3-4 has a mean of 14.3 and standard deviation of 4.6. The graph at the top of Figure 8 shows a greater proportion of rejected batches (red points) than passing batches (blue points) in this subgroup. The middle branch of the decision tree defined by V15 >= 0.4 and V21 < 0.9 yields a distribution of % at stage 3-4 with a mean of 20.4 and standard deviation of 2.1. Just one of the 36 batches processed this way results in a rejected lot.

The decision tree model was built by excluding 72 (30%) of the 240 batches, these excluded batches were used to validate the decision tree. The partitions defined by the levels of V15 and V21 in the decision tree explain 40% of the variation in % at stage 3-4 of the 72 batches that were excluded from building the model. Nine of the 72 model validation batches met the criterion of V15 >= 0.4 and V21 < 0.9 with all nine of these batches passing the compliance test. Thus, V15 and V21 are verified as being strongly associated with some of the excessive variation in % at stage 3-4 and are potential drivers of resultant batch failures.

Recursive partitioning is a good visualization tool to help all consumers of process data see and communicate understanding about the dominant drivers of product variation; however, the method requires a large number of batches to reliably build decision trees with a greater number of branches (possibly utilizing other input variables to define the additional branches). Nonetheless, it is a great tool for aiding understanding and communication about the potentially dominant drivers of a problem.

To determine if there are additional input variables that may enable us to further reduce variation in % at stage 3-4, a PLS analysis was performed using cross validation. The coefficients from the resulting model are illustrated in Figure 9. The area of each rectangle of the Tree Map is in proportion to the size of the PLS model coefficient for the corresponding input variable. Blue rectangles stand for negative coefficients and red for positive coefficients. Two dominant factors, in addition to V15 and V21, are identified as V9 and V18. The sign of these four model coefficients tell us that increasing the values of V9 and V18, and reducing the values of V15 and V21 will result in higher values of % at stage 3-4.

Table A compares the observed vs. predicted result of the batch acceptance test, based on 72 batches that were excluded from the model fitting. The PLS model predicts batch performance of the 72 batches excluded from the model with three misclassifications. However, as a prediction model of batch performance, the center branch of the decision tree in Figure 8 works just as well as a predictive model of batch failures in helping to reduce future occurrences of batch failures. With nine of the 72 model validation batches meeting the criterion of V15 >= 0.4 and V21 < 0.9 and with all nine batches passing the compliance test, the recursive partitioning decision tree appears to be a simpler and sufficient predictor of batch failures.

To investigate in greater detail the effects of the input

Figure 9. Tree map of PLS model coefficients.

factors V9, V15, V18, and V21 on % at stage 3-4, a D-optimal DOE with a full quadratic model was performed. The resulting DOE worksheet is presented in Table B.

Summary results for the DOE analysis are presented in Figure 10, which shows significant linear effects of all four factors and a significant interaction between V15 and V21 at the 5% level. The direction of the relationship between % at stage 3-4 and each of the four inputs is in agreement with the sign of the coefficients from the PLS model. Multiple optimum solutions that get the mean of % at stage 3-4 on target exist, one of which is to operate close to V9=0.25, V15 = 0.4, V18 = 0.9, and V21 = 1.2. To explore the viability of this solution, the regression model was used to simulate the propagation of variation from the four inputs when set at the above values with a tolerance as indicated in the bottom part of Figure 10, and random batch to batch variability defined by a standard deviation of 0.5 (more than twice the standard deviation of the residuals in the fitted regression model). This predicts a distribution of % at stage 3-4 wholly within the required range (Figure 10) with a predicted sigma quality level of 4.8. In practice, before accepting this solution, it would be necessary to validate the model and predicted behavior with model validation batches performed at or within the proposed tolerance of the four process settings.

Summary

The blend of three key technology enablers – measurement, data integration, and data analysis systems – required to improve product quality through increased process understanding, depends upon the circumstances of the particular manufacturing facility.

Mature manufacturing facilities are unlikely to have extensive inline, at-line, or online measurement systems in place for tracking process inputs. Thus, the adoption of effectiveness modeling is a way to improve product quality through increased process understanding. The focus is to identify the critical few inputs and to develop empirical models of the effects of these on product quality that approximate the causal relationships between inputs and product quality. These models are then deployed to reduce variation

in final product quality and achieve performance requirements through improved process and material specifications and controls. A subset of some visual and statistical effectiveness modeling techniques in the context of mature manufacturing was illustrated in Case Study 1.

Manufacturing facilities for newer products are more likely to have extensive inline, at-line, or online measurement systems for tracking process inputs. The path to improved product quality through increased process understanding is a combination of efficiency and effectiveness modeling. Efficiency modeling methods are deployed to predict product performance, define some temporary controls to reduce batch failures, while effectiveness studies are conducted. The efficiency models also help identify and prioritize the inputs to be investigated in detail through effectiveness modeling techniques. The combined use of efficiency and effectiveness models may help reduce the number of process inputs that are routinely measured to the critical few if this helps accelerate cycle time or reduce other risks. A subset of some efficiency and effectiveness techniques in the context of a data-rich measurement environment was illustrated in Case Study 2.

Quality by Design is effectiveness modeling applied in process R&D, where it is possible to explore wider ranges of process inputs. The goal is to design a robust process that identifies the critical few inputs and tolerances for each key input that must be maintained in manufacturing. From a measurement systems viewpoint, the goal is to define the few inputs that must be measured or controlled in manufacturing and to achieve this knowledge through a high level of process understanding.

Simplifying data analysis and reporting is critical if more people in process development and manufacturing are to interpret and communicate around models that enhance process understanding. This article has introduced visual modeling methods that are easy to deploy for mainstream

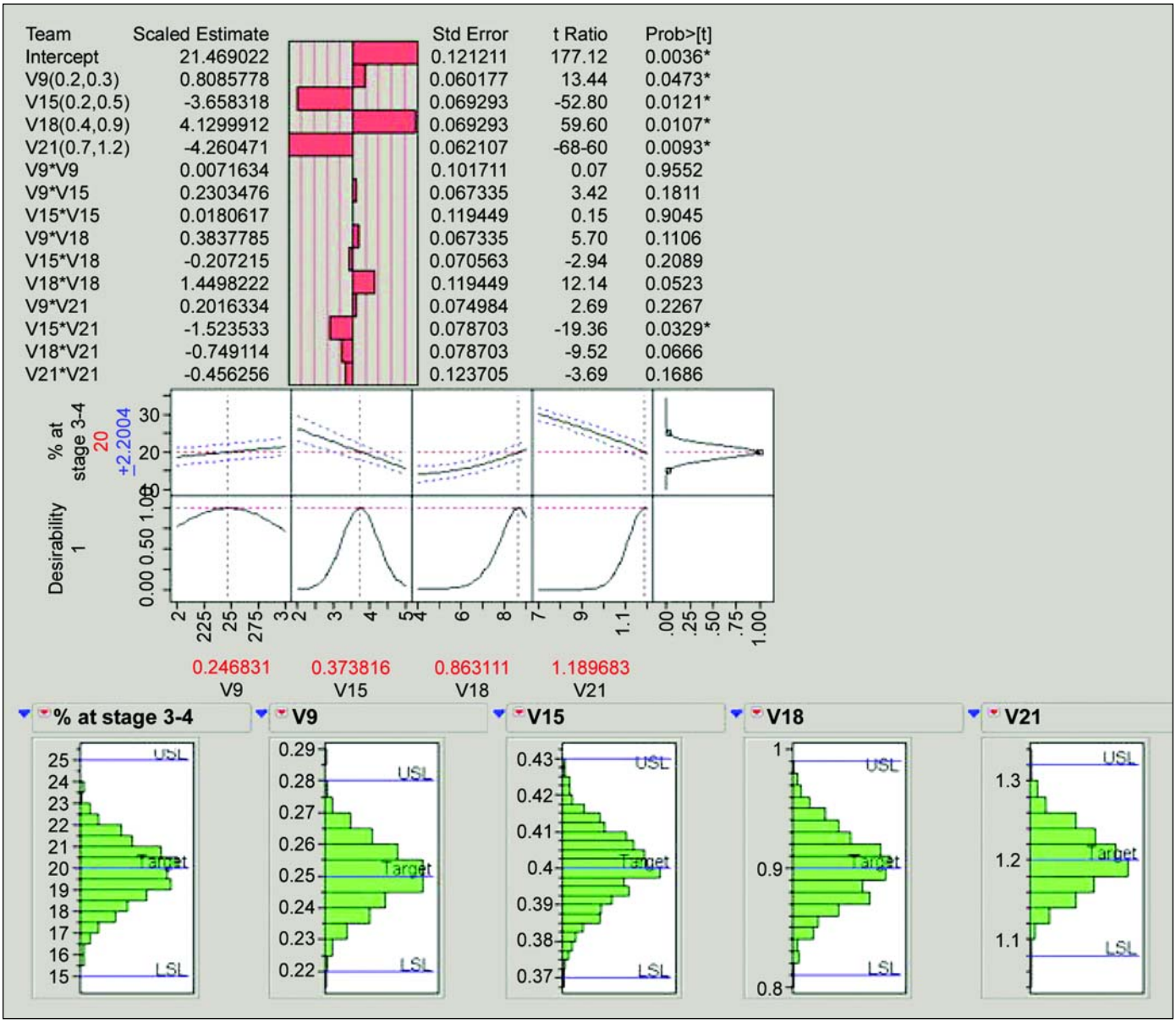


Figure 10. DOE summary analysis.

users and help them apply the principles of statistical thinking, particularly those of modeling variation in process outputs and identifying the key drivers of process variation.

About the Author

Dr. Malcolm Moore has worked with clients to integrate statistical methods and software into R&D, quality improvement, defect reduction, cycle time reduction, and corporate Six Sigma consulting activities for a variety of industries, including pharmaceutical and semiconductors. Prior to joining SAS UK, he worked at Light Pharma, BBN, Astra Zeneca, and lectured in medical statistics at Newcastle University. He is an expert in design of experiments, and received his PhD in design of non-linear experiments at London University. He can be contacted by e-mail at: malcolm.moore@jmp.com.

SAS Institute, Whittington House, Henley Road, Medmenham, Marlow SL7 2EB, United Kingdom.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Introduction to Real Time Process Determination

by Kim Walter

This article introduces a state-of-the-art method to track conditions for wet processes that provides continuous operating guidance through a combination of measured and calculated values.

Many processes in the pharmaceutical industry require mixing of active pharmaceutical ingredients with inactive powders to transform the mixture into useful solid dosage material. Frequently, the process incorporates the use of water or organic solvents, the so-called wet processes such as drying of granules from a mechanical mixer, spray granulation of the product in a fluid bed, pellet coating for taste masking, pellet coating to modify drug release characteristics, and powder laying of the active drug on an inactive powder.

To produce to specification, wet processes generally require control of the humidity in the process chamber, although in some cases, control of temperature or partial pressure is critical. For organic solvents, instruments cannot measure the relative humidity inside the process vessel. Common practice is to use a trial and error procedure, changing process conditions until all parameters are within tolerances. This procedure is both difficult and wasteful, depending mostly on the insight and decisions of process developers and experienced operators.

Real time process determination™ is a state-of-the-art method to track conditions for wet processes that provides continuous operating guidance through a combination of measured and calculated values. It may be used to control a continuous or a batch process through all of its steps and transitions, regardless of variations in ambient or process conditions. It gives the skilled process developer easy-to-interpret information in the form of a chart that guides the decision process.

Process Variables

Pharmaceutical production demands consistent results, which are very difficult to achieve with batch processes since each batch is slightly different. To apply real time process determination, the target conditions must be defined - endpoint humidity for drying, solvent encapsulation and applied membrane characteristics for pellet coating, residual moisture in tablet pressing, etc. Theoretically, if the process variables are consistently on target, the specifications of each batch will be identical.

However, running a process in precisely the same way time after time is impossible, and even very small deviations can have a significant influence on the end result. Different response times for the process variables also may be a factor when adjustments are made during production - a change in the spray rate affects the process nearly instantly, while a change in the inlet temperature has a much longer response time.

A preferred thermodynamic condition exists in the process chamber in order to achieve consistent results. Using coating and spray granulation as an example, variables are feed rate, inlet temperature, and spray rate of solvent. The thermodynamic condition can be given as a particular combination of relative humidity and temperature - the target condition. In this case, only two process variables must be controlled during the process instead of all three. In some processes, one of these conditions, relative humidity or temperature, may be more critical than the other. Therefore, the critical variable becomes the primary target condition and the not-so-critical variable becomes the secondary target condition, enabling the critical target condition to be reached faster. If there is a deviation in the target temperature in the process chamber - the process variable with the longest response time - the spray rate can be adjusted, which has the shortest response time, which will change the temperature nearly instantly. The process gas flow rate can be changed, which has a median response time, if we want the target temperature to react over a short time interval.

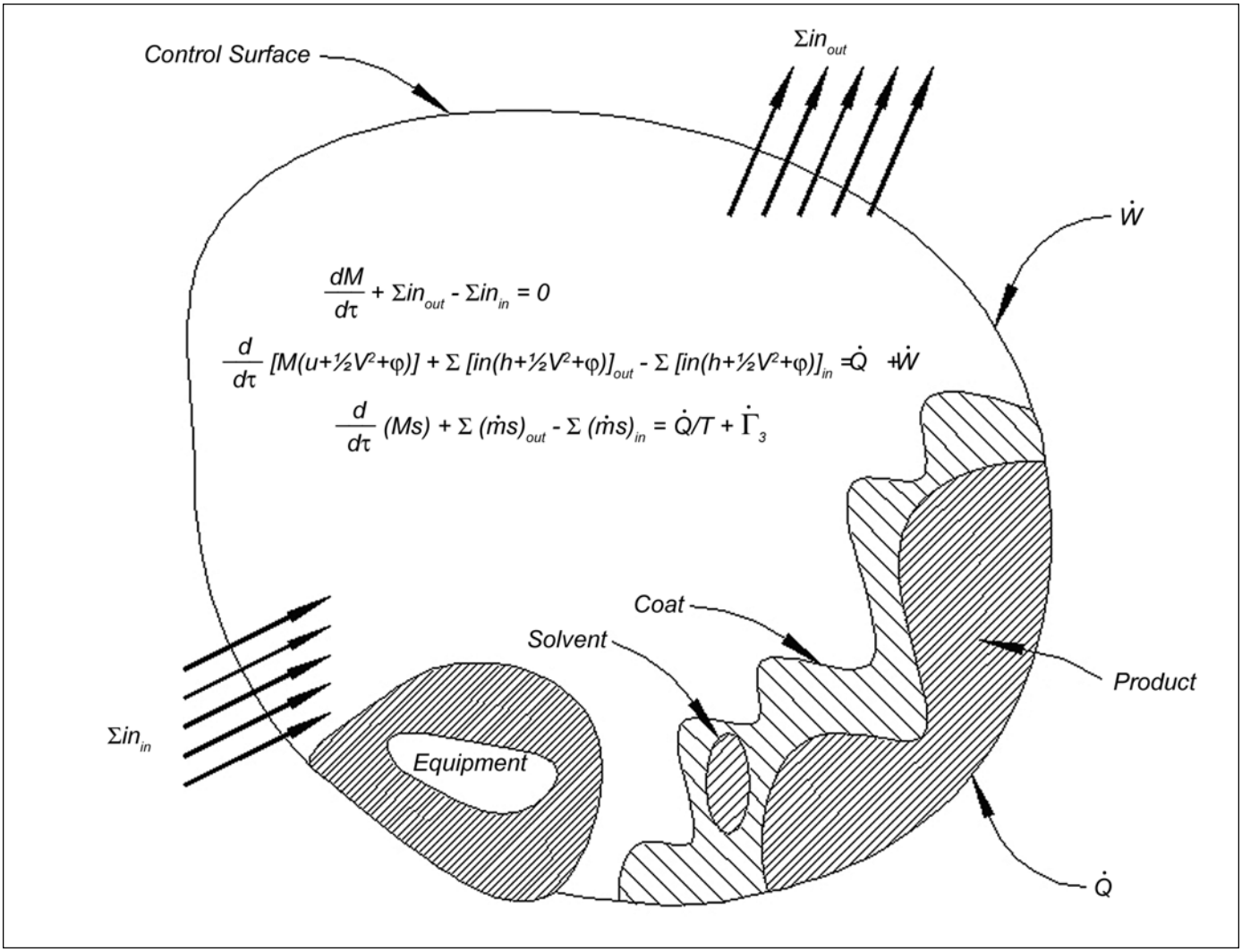


Figure 1. Thermodynamic model for real time process determination.

Usually, only the process variables are controlled, without knowing the thermodynamic target. However, if thermodynamic laws are applied to the equipment, the thermodynamic condition in the process chamber can be determined, and by experimenting with different conditions, the critical thermodynamic condition can be determined. With the critical thermodynamic condition specified, the scale-up and transfer from equipment to equipment become easier. Choosing the thermodynamic condition for controlling the process, instead of using only the single loop recipe control, will ensure more reproducibility of both batch and continuous processes. This is the basic objective of real time process determination.

The Thermodynamic Approach

The thermodynamic approach is built on two fundamental laws, conservation of mass and conservation of enthalpy. The law of conservation of mass says that the change of mass inside a closed system in time is equal to the flux of mass entering the closed system minus the flux of mass exiting. The law of conservation of enthalpy says that the change of enthalpy inside a closed system in time is equal to the flux of enthalpy entering the closed system minus the flux of enthalpy exiting.

Figure 1 shows the heat and mass balance of the thermodynamic system used on the process equipment. The control surface represents the equipment walls. Through the inlet enters some mass flow of process gas, atomizing gas, spray liquid (which may consist of several solvents), solvent vapor in the process gas, and solids suspended or dissolved in the spray liquid. Through the outlet flows the process and atomizing gases, which will contain some solvent vapor. The difference in the mass flow of solvents from the inlet to the outlet is what is added or removed from the product over time. The amount of solvent inside the equipment, which is not evaporated, is depicted as an area on the drawing.

The enthalpy balance consists of the enthalpy flowing out minus the enthalpy flowing into the equipment. The divergence in the enthalpy flow is the change in the enthalpy level inside the equipment and the heat flow "Q" through the equipment wall. The term "W" depicted on the drawing is the work done on the system.

The last thermodynamic term we need to understand is adiabatic. A process is adiabatic when the heat change inside the closed system happens without exchange of heat with the surroundings. When the process is adiabatic, the enthalpy is constant. So if the heat loss from the equipment is identified,

the exchange of the enthalpy inside the equipment walls can be calculated.

Equations to Determine Physical Values

Five physical values are important to the process:

1. The temperature, which can be measured.

2. The pressures, including ambient pressure, total pressure, and partial pressures of each component. The total pressure is the sum of the partial pressures of each individual gas and the partial vapor pressure of the solvents. The partial solvent pressure (vapor pressure) is the amount of the particular solvent present in the gas. The saturated vapor pressure is the maximum pressure the particular solvent can have at a given temperature.

3. The concentration of solvent, also called the specific humidity – the mass of the particular solvent dissolved per mass unit of gas.

4. The dewpoint temperature, at which, for a given solvent concentration (specific humidity) and total pressure, the gas/solvent mixture is saturated.

5. Specific heat capacity - the amount of heat necessary to increase a mass unit of the product, the particular solvent as vapor or liquid, and the gas, one degree.

To connect the thermodynamic laws, the equations of the five physical values must be used. The relative humidity is calculated as the ratio between the actual specific humidity and the saturated specific humidity in percent for a given gas temperature. The relative humidity also is the ratio between the actual vapor pressure and the saturated vapor pressure in percent for a given gas temperature. The relative humidity for the solvent {*i*} is expressed by the equation:

$$\varphi_{solvent\{i\}} = \frac{p(partial\text{-}pressure)_{solvent\{i\}}}{p(saturated\text{-}pressure)_{solvent\{i\}}}$$

For water, there are instruments that measure the electric resistance of the air, which depends on the concentration of water vapor. This measurement, in combination with the air temperature, enables the calculation of the relative humidity for water vapor. Since instruments cannot measure the relative humidity of an organic solvent; it must be calculated.

The relation between the relative and the specific humidity can be calculated:

$$x_{solvent} = \frac{M_{solvent}\,\varphi_{solvent}\,p(saturated)_{solvent}}{M_{gas}[p_{total} - \varphi_{solvent}\,p(saturated)_{solvent}]}$$

where $M_{solvent}$ is the molecular weight for the particular solvent and M_{gas} is the molecular weight of the process gas.

The enthalpy, the heat content of a mass unit of gas, is calculated as the specific heat capacity of the gas plus the sum of the specific humidities of the solvents times their specific heat capacities, taking the entire sum times the temperature plus the specific humidity of the solvents times their heats of evaporation.

$$h = \int_{T_{ref}}^{T} [c_{p_{gas}}(T) + \sum_{i=1}^{i=n} x\{i\}_{solvent}\, c_{p_{sol}}(T)]dT + \sum_{i=1}^{i=n} x\{i\}_{solvent} r_{solvent}(T_{ref})$$

The term x{*i*} is the mass ratio of the particular solvent {*i*} dissolved as vapor in the process gas. The total pressure of the gas plus the sum of the partial pressures of the solvents, which is the ambient pressure, is constant. When the solvents are dissolved in the gas, the gas volume will expand, lowering the density of the gas. If the solvent is water, the change in density of the gas is negligible since the amount of water vapor that can be dissolved before the mixture becomes

M	= sum of mass (product, equipment, coat, solvent, and gas) inside the control volume [kg]
t	= time [sec]
$\dot{m}_{in}$	= mass flow into the control volume [kg/sec]
$\dot{m}_{out}$	= mass flow out of the control volume [kg/sec]
u	= inner energy [Joule/kg]
h	= enthalpy [Joule/kg]
V	= velocity [m/sec]
s	= entropy [Joule/kg]
$\dot{Q}$	= heat [Joule/sec]
$\dot{W}$	= work [Joule/sec]
$\dot{G}_s$	= entropy production [Joule/Kelvin*sec]
$\varphi_{solvent\{i\}}$	= relative humidity for the solvent {i} [%{saturated}]
$p(partial)_{solvent\{i\}}$	= partial pressure of solvent {i} [Pascal]
$p(saturated)_{solvent\{i\}}$	= saturated pressure of solvent {i} [Pascal]
p_{total}	= sum of the gases and solvents partial pressure [Pascal]
$x_{solvent}$	= general mass ratio between particular solvent and the gas [kg/kg]
$M_{solvent}$	= molecular weight of the solvent [kg/kmol]
M_{gas}	= molecular weight of the process gas [kg/kmol]
h	= enthalpy, heat content per mass unit of gas [Joule/kg]
T	= temperature [Celsius] or [Kelvin]. If Kelvin is used in the enthalpy equation, all values have to be expressed in Kelvin
T_{ref}	= chosen reference temperature, normally 0°C
$c_{p_{gas}}$	= specific heat capacity of the process gas [joule/kg*8C]
$c_{p_{sol}}$	= specific heat capacity of the solvent vapor [joule/kg*8C]
$\dot{s}\{i\}_{solvent}$	= mass flux of the solvent {i} entering the control volume as liquid into the control volume [kg{solvent}/sec]
$x_{product}$	= specific humidity on product surface in a coating process
$x_{ambient}$	= ambient specific humidity [kg{solvent}/kg{gas}]
$\dot{m}_{process\text{-}gas}$	= flux of process gas mass flow rate entering or leaving the control volume [kg{gas}/sec]
$r_{solvent}$	= heat of evaporation for the solvent at the reference temperature [Joule/kg{solvent}]

Table A. Nomenclature.

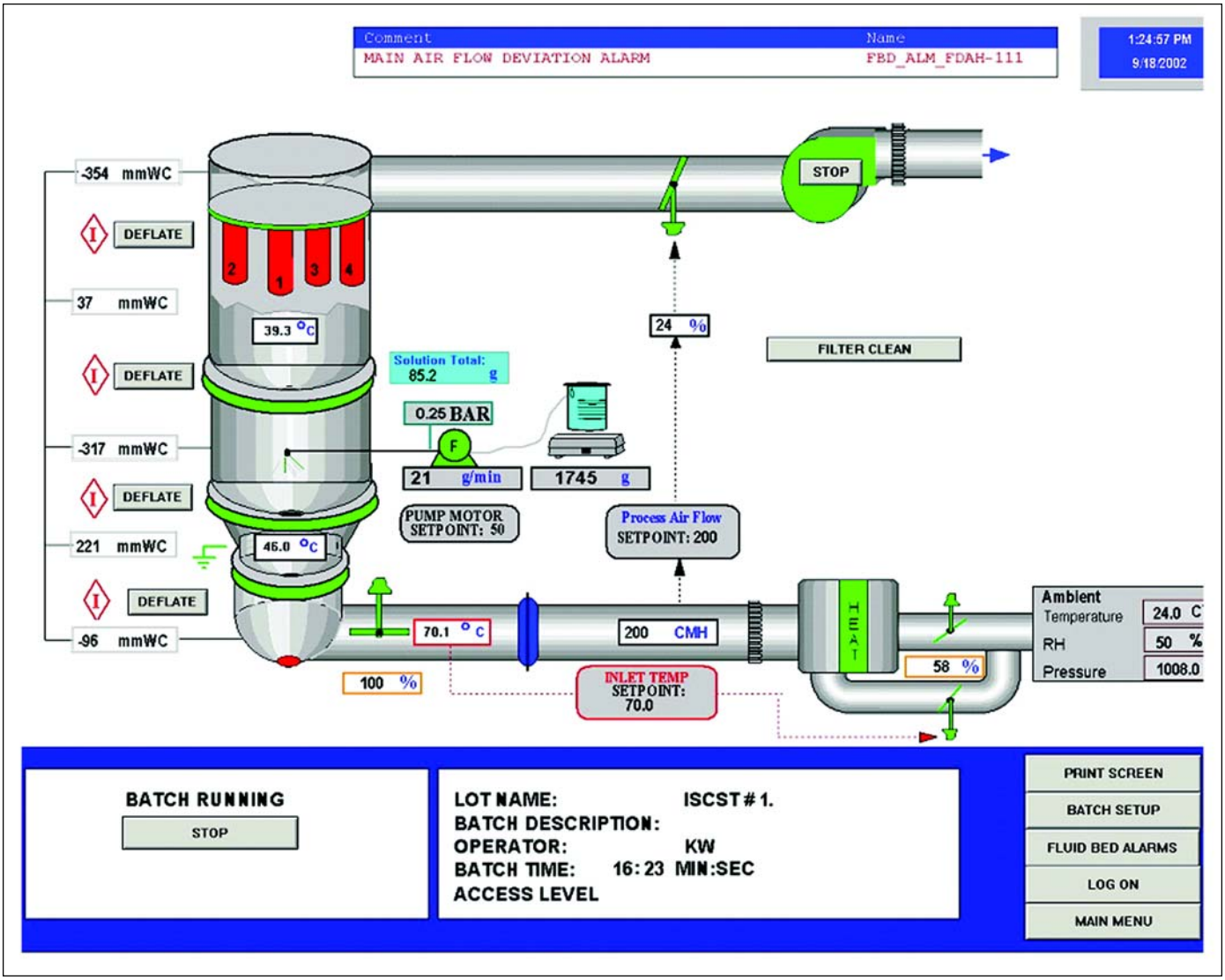


Figure 2. Automation control screen for typical multi-purpose process equipment.

saturated is small. When a mixture of solvents is present during the process and some of the solvents are volatile, the change in gas density has to be taken into consideration. The enthalpy gives the value of the gas and the vapor heat content, calculated from a chosen reference temperature, T_{ref}, which normally is the triple point of water 0°C. The term $r_{solvent}$ in the equation for the enthalpy is the evaporation heat for the particular solvent {*i*} at the reference temperature.

All the values in these three equations are physical material properties and are a function of the temperature. The values have been measured by many people over the last hundred years, published in tables, and organized as a physical-chemical database. Over time, many have converted the physical-chemical data table into mathematic formulae with the use of different approximations. The equations that approximate the physical-chemical data seem at first glance complicated. However, with current computer capacity, the task is possible.

With a further analysis of the three equations, it can be concluded that if two of the four values are known, the two other values can be calculated. However, if all four values are known and two values are enough to determine the thermodynamic condition, it produces six different ways to solve the equations. This sounds strange, because if the values are known, why calculate them? The answer is: there is more information from the normal control system than is needed to determine the thermodynamic condition. This allows us to determine the unknown values in the thermodynamic models, such as heat loss, heat exchange, measuring errors, and so on.

Determining the Thermodynamic Condition

For a given process, the inlet, product, and outlet temperatures from the control system can be obtained. The flow rate of process gas is known, as is the concentration of solvent in the inlet gas (known from the inlet gas dewpoint temperature). Again, using spray granulation or coating as an example, the amount of solvent added to the process is known. The ambient pressure is either measured or can be assumed to be normal atmospheric pressure, 1013 hPa.

The first calculated value is the enthalpy of the inlet gas.

The equipment is started empty, with a given inlet temperature and process gas flow rate, and observed. In an adiabatic process, the product and outlet temperatures should rise to the inlet temperature as the equipment warms up. This is not the case; the system or the equipment is non-adiabatic for two reasons: the heat loss through the equipment wall and the heat transfer from the process gas to the equipment, both of which change the temperatures. The product and outlet temperatures will start out lower than the inlet temperature and gradually increase as the system reaches a steady state. After some time has elapsed, the product and outlet temperatures will approach fixed values. At this point, the outlet temperature will normally be lower than the product temperature. Two important inherent features of the particular equipment being tested has been observed: the time response and the effect of the heat loss through the equipment wall, both unique for this equipment. By repeating this procedure with different process gas flow rates and inlet temperatures, the heat loss of the particular installation can be determined. If the same procedure is executed with different products and product loads, information is determined about the total system's heat loss and time response. The heat loss can then be calculated, so with both the equipment running empty and with product being processed, the real inlet temperature can be determined.

The next investigation should be the accuracy of the process gas measurement. Measuring the flow rate is difficult and frequently inaccurate. The best example to use in an investigation of the gas flow measurement is coating. In the coating process, processing time is normally long enough for the equipment to reach steady state. With the knowledge about the heat loss, the real inlet enthalpy is known. In coating, a small amount of residual solvent is encapsulated in the coat; therefore, the process is close to adiabatic. Assuming an adiabatic process, the enthalpy of the inlet and the enthalpy on the surface of the product must be the same. Using the equation for the inlet condition with the modified inlet temperature, the specific humidity of the inlet gas, and the rate of process gas, the inlet enthalpy is known. Measuring the product temperature and the spray rate, the relative and specific humidity on the product surface can be determined. The specific humidity on the product surface is the ambient specific humidity and the added solvents from the spray divided by the process gas mass flow rate:

$$x_{product} = x_{ambient} + \frac{\sum_{i=1}^{i=n} \dot{s}\{i\}_{solvent}}{\dot{m}_{process\text{-}gas}}$$

Performing this procedure with different process gas flow rates and spray rates will reveal the deviation between the measured process flow and the actual flow rate. With the two corrections, the heat loss and the deviation between the measured and calculated process gas rate, the relative humidity in the process chamber can now be calculated at any given time.

The customary control procedure in coating is to adjust the spray rate according to the product temperature. The product temperature is governed by the spray rate and the time response due to the thermal heat exchange between the process gas and the equipment and product mass. The product temperature is measurable and real and the calculation of the specific humidity, based on the equation, will give the actual relative humidity on the product surface. Combining the "two" relative humidities, one based on constant enthalpy and one on spray rate/process gas mass flow, will provide the adiabatic ratio, or how far the process is from adiabatic. When the steady state is reached, the adiabatic ratio equals one.

Using the Thermodynamic Calculation to Guide the Process

The thermodynamic calculations utilize the information from the control system. Determining the numerical values from the equations is complex and time consuming, so the obvious choice is to use a computer program. When this is written and data are input from the control system, the logical step is to bring the computer program and the control system together as one unit and calculate the thermodynamic conditions in real time. With the real time calculation, the program also can calculate how much each of the process values has to be changed to bring the process to the target conditions. The program calculates all possible changes and the consequence of each single change. There are a total of 12 changes and eight consequences to choose among, depending on which final thermodynamic condition the process demands. The final challenge is to display the possible choices in a comprehensive way.

Instruments make available information visible, putting the operator in the best possible position for making an optimal decision. Figure 2 shows a control screen for a typical multi-purpose process scheme. This familiar configuration uses a combination of flow diagram and equipment schematic to display measured physical conditions such as temperature, pressure, and flow rates, as well as setpoints for process variables.

To display calculated conditions in addition to measured, a real time process determination screen may be added to the control panel - *Figure 3*. In the case of bottom spray coating, where the relative humidity in the process chamber has the highest priority, the value can be calculated and displayed. Because the change in the relative humidity is a result of changes in three other process variables (inlet temperature, solution spray rate, and process gas flow rate) the deviation meter shows the results from the calculation and displays the proper action to take. The operator can, in a single glance at the meter, take in all three values which can be changed (the gold-colored lines), and how much each of the values has to be changed to reach the desired condition.

Experience dictates that the combination of analog and digital displays is the best way to notify the operator about current and desired conditions. On the deviation meter, the three set points are shown both graphically and digitally. Because bottom spray coating is a dynamic process with a long response time for one of the observed values (the process

chamber temperature), the operator also has to be informed about the time development of the process. This also is a combination of analog and digital information. The digital information is given by the adiabatic ratio. This is calculated as a ratio between the evaporation rate (based on a combination of the spray and process gas rates) and the measured temperature difference between the inlet and process chamber temperature. This number provides information on the current adiabatic ratio, but to make the dynamics of the adiabatic ratio visible, a new method had to be developed.

The Adiabatic Ratio Instrument

The layout of the adiabatic ratio instrument has been influenced by the opinion that few persons can comprehend values that are not given in a linear form. Some observers even go as far as to say that no person can comprehend magnitude. We seem all better equipped to comprehend linear changes than changes in magnitude.

Relative humidity is based on the saturated vapor pressure as a function of temperature. The saturated vapor pressure increases with around the sixth power of temperature; therefore, a small increase in temperature creates a large change in relative humidity. The aim has been to find a way to display the relative humidity in linear form. The solution is a dynamic psychrometric chart or the dynamic specific humidity diagram - *Figure 3*.

The Thermodynamic Equations

Figure 1 represents the basic thermodynamic system for a control volume. The three equations are conservation of mass, conservation of enthalpy, and increase in entropy.

The control surface is an imaginary boundary, chosen so that the fluxes crossing the boundary are known values or can be determined. The fluxes are the mass flow, $\sum \dot{m}$, the sum of all gases, vapors, liquids, and solids flowing in and out of the control volume. The term $\dot{W}$ is the work applied to the control volume. In this specific case of real time process determination, the work applied is the movement of the process gas and the product inside the control volume, in short: the pressure loss experienced by the fan. The term $\dot{Q}$ is the heat passing over the boundary of the control volume. In the case of real time process determination, the heat is the heat loss through the equipment wall.

The first equation, conservation of mass, expresses the change of mass in time inside the control volume plus the flux of mass out minus the flux of mass in. This is equal to zero. The mass inside the control volume is represented by M, where M is the sum of the equipment wall, the product, the solid delivered to the product as coat or layering material, and the solvent retained in the product, coat, or applied material (all the solvent that has not evaporated).

The second equation, conservation of enthalpy or the first law of thermodynamics, expresses that the change of enthalpy in time inside the control volume plus the flux of enthalpy out minus the flux of enthalpy in, is equal to the delivered heat and work flux to the control volume. The term $(u + \frac{1}{2} V^2 + n)$ is the energy. The u is the internal energy of all the material inside the control volume except the kinetic energy and potential energy. The numerical value of u is assumed to be zero at the temperature scale zero point. The term $\frac{1}{2} V^2$ is the kinetic energy of the material inside the control volume, where V is the velocity. The n is the chemical potential of the material inside the control volume. The term $(u + \frac{1}{2} V^2 + n)$ is expressed in joules. In the term representing the mass flow in and out of the control volume, the internal energy u is replaced by h, $(h + \frac{1}{2} V^2 + n)$, where h is the heat content of the material entering and leaving the control volume.

The third equation, increase in entropy or the second law of thermodynamics, expresses that the change of entropy in time inside the control volume plus the flux of entropy out minus the flux of entropy in, is larger than the heat conveyed over the boundary of the control volume divided by the control volume's absolute temperature.

$$\frac{d}{dt}(Ms) + \sum (\dot{m}s)_{out} - \sum (\dot{m}s)_{in} \geq \frac{\dot{Q}}{T}$$

In order to balance the equation, the production of entropy inside the control volume must be added. The term $\dot{G}_s$ expresses this production of entropy inside the control volume in joule/KelvinBsec. The M, $\dot{m}$ and $\dot{Q}$ are the same as in the first and second equations. The s is the entropy from Gibbs equation. For the determination of the entropy difference between the entering and exiting flow, we look at an example. For a simple compressible substance s = s(u,v), the entropy s is a function of the inner energy u and the volume per unit of mass v. Differentiate the function and we obtain:

$$ds = \left(\frac{\partial s}{\partial u}\right)_v du + \left(\frac{\partial s}{\partial v}\right)_u dv$$

Using the thermodynamic definitions of temperature and pressure, we find:

$$ds = \frac{1}{T} du + \frac{P}{T} dv$$

Therefore the difference between the entropy s{out} and s{in} is:

$$s_{out} - s_{in} = \int_{u_{in}}^{u_{out}} \frac{du}{T} + \int_{v_{in}}^{v_{out}} \frac{P}{T} dv$$

The entropy s is expressed as joule/Kelvin.

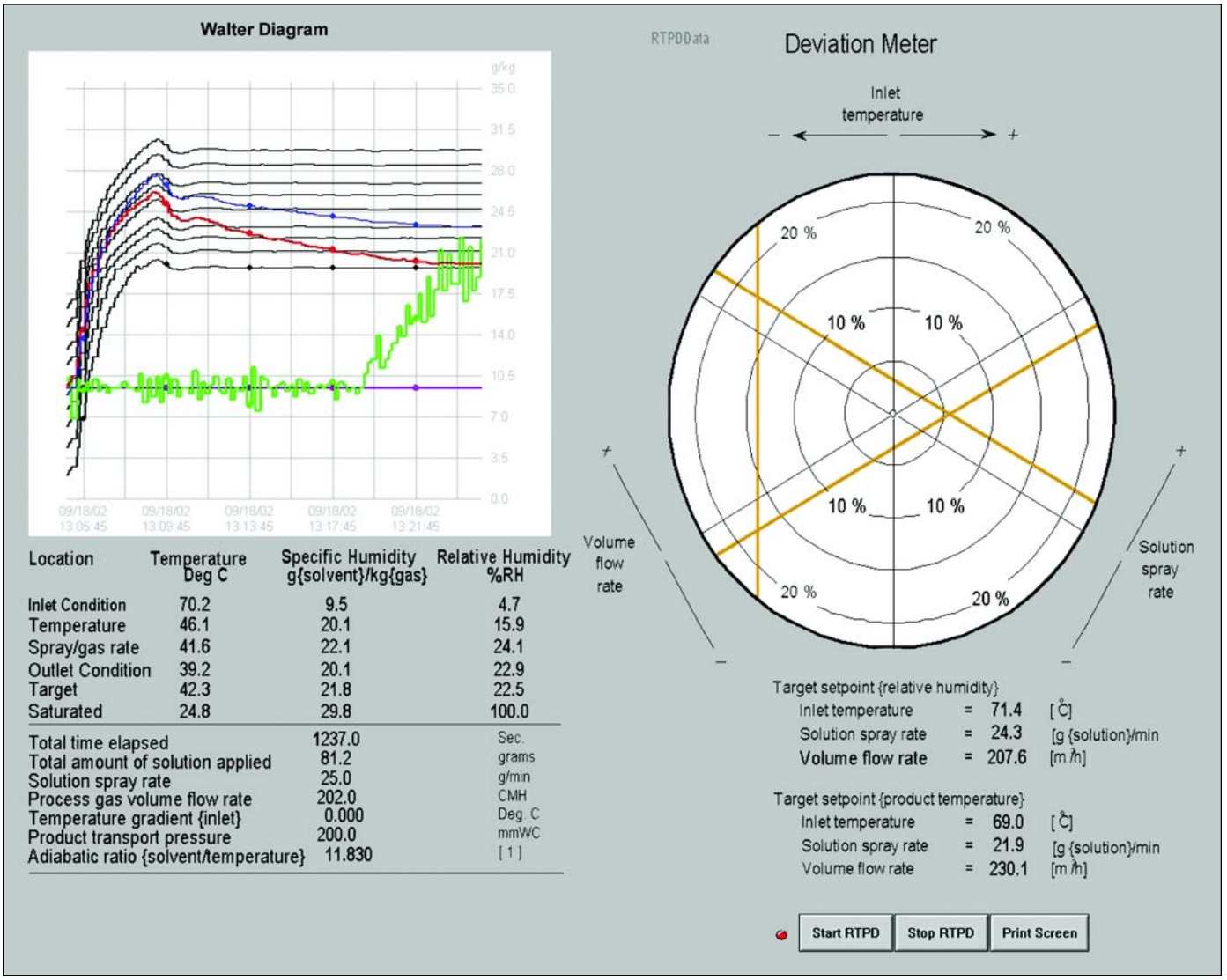
Along an adiabatic line, the temperature and the specific humidity are nearly linear. So if the values of the ambient condition, inlet, process chamber, and outlet conditions are represented as the specific humidity and used as ordinate, the relations of these conditions are linear. Now the specific humidity of each relative humidity value along the inlet enthalpy line can be calculated. The 100 percent relative humidity, or saturated condition, gives the maximum ordinate value. The abscissa value is time. From testing it is known that the time response is from 20 to 45 minutes so this is the length of the chart. The background of the chart is the relative humidity expressed as specific humidity.

The process conditions - ambient condition, inlet, process chamber, and outlet condition - are shown in relation to the relative humidity. As the inlet temperature increases, the saturated value of the specific humidity increases also, so the dynamic psychrometric chart grows. When the inlet temperature decreases, the saturated value of the specific humidity also will decrease, so the chart shrinks. When the process is adiabatic, the specific humidity based on the spray/process gas flow rate and the specific humidity of the process chamber temperature will be equal, so the two curves will overlap. When the process is non-adiabatic, the specific humidity of the combined spray/process gas flow rate and the specific humidity of process chamber temperature will be two different values, so the two curves will be separated.

With one glance at the dynamic psychrometric chart, the operator can evaluate if the process is adiabatic or non-adiabatic, and how far from adiabatic the process is in the current situation. Thus, the operator sees information in a linear form indicating how much the spray rate can be increased by evaluating the distance from the ambient condition to the curve showing the specific humidity of the spray/process gas flow rate with the specific humidity line representing the target relative humidity. People who have worked with the system find the dynamic psychrometric chart easy to understand and say that it makes the decision process fast and easy.

An Example of Real Time Process Determination

Using the example of a bottom spray coating process, the thermodynamics process screen contains both actual and



Location	Temperature Deg C	Specific Humidity g{solvent}/kg{gas}	Relative Humidity %RH
Inlet Condition	70.2	9.5	4.7
Temperature	46.1	20.1	15.9
Spray/gas rate	41.6	22.1	24.1
Outlet Condition	39.2	20.1	22.9
Target	42.3	21.8	22.5
Saturated	24.8	29.8	100.0

Total time elapsed	1237.0	Sec.
Total amount of solution applied	81.2	grams
Solution spray rate	25.0	g/min
Process gas volume flow rate	202.0	CMH
Temperature gradient {inlet}	0.000	Deg. C
Product transport pressure	200.0	mmWC
Adiabatic ratio {solvent/temperature}	11.830	[1]

Figure 3. Thermodynamics process screen.

target process variables in both graphical and digital form - *Figure 3*. The deviation meter at the right shows that the inlet temperature (gold line) should be increased 15% to achieve the desired thermodynamic condition. Alternatively, the solution spray rate could be decreased less than five percent or the volume flow rate could be increased by less than five percent. Below the deviation meter are the calculated numerical target setpoints for inlet temperature, solution spray rate, and volume flow rate.

The current process values are given at the left side of the screen, below the graph. The inlet temperature is 70.2°C, and the deviation meter shows that a change of the inlet temperature to 71.4°C will give the desired relative humidity. Likewise a change in solution spray rate from the actual 25.0 g{solution}/min to the target 24.3 g{solution}/min will produce the desired condition. A third possibility is to change the volume flow rate from the current 202 m^3/h to 207.6 m^3/h.

The graph on the left side is the dynamic specific humidity diagram (Walter diagram). All the process values are calculated as the specific humidity along the adiabat that goes through the inlet condition. The violet line is the ambient condition, less than 10 g{water}/kg{air}, which is a dewpoint temperature of 14°C. The green line is the addition of water or solvent from the solution spray rate. Until 12 minutes ago, the green line was overlapping the violet line, which indicates that no spraying was occurring.

The black lines represent where the relative humidity values cross the constant enthalpy line or adiabat. The upper black line is the saturated humidity. The left side of the graph shows the specific humidity of the saturated line, which is approximately 16 g{water}/kg{air}. This indicates that 6 g{water}/kg{air} adiabatic could be added to the ambient gas before the gas would become saturated. The saturated line grows over the next four minutes to a specific humidity of 31 g{water}/kg{air} as the inlet temperature increases. The saturated line decreases when the inlet temperature passes the setpoint as the temperature controller begins to take over. The temperature under-shoots and reaches the final inlet temperature in less than four minutes. The other constant relative humidity lines parallel the saturated specific humidity line.

The red line represents the product temperature. The line has the same initial value as the violet line, which is the ambient condition. The inlet gas flow is cooled by the inlet duct and equipment plenum and delivers heat to the product. This is a non-adiabatic situation, because there is heat exchange with the surroundings. Initially, the product temperature is between the fourth and the fifth relative humidity line. As the heat is delivered to the equipment and product, the product temperature line decreases to the level of the ninth relative humidity line. If the relative humidity could be measured inside the process chamber, it would show a similar decrease during the elapsed time, real physical behavior.

The blue line represents a modified outlet temperature. Since the specific humidity of the outlet temperature is the same as the specific humidity of the product temperature, the two lines should overlap. So the outlet temperature line is modified by calculating the relative humidity of the outlet temperature based on the cooling with constant specific humidity (the product specific humidity), providing information on the relative humidity in the outlet of the process chamber where the filter is located. In top spray granulation, the outlet temperature line indicates when the relative humidity is high at the filter, which can produce tacky product that will begin to block the filter. In bottom spray coating, the blue line can cross the red line, which means that the product temperature is lower than the outlet temperature. This occurs when the solvent is not totally evaporated from the coat during the free flight of the product, causing an increase of the solvent content in the product. The coat will become tacky and the product load will start to lump together, bringing the coating process to a standstill.

The graph shows that the spray pump was initiated eight minutes ago, because the specific humidity value increased, as shown by the increase of the green line. The difference between the violet line and the green line is the addition in specific humidity due to the spraying. It was observed that the red line (the product temperature) stops decreasing after the green line has reached the same specific humidity as the specific humidity of the product temperature.

The numerical values at the current condition are below the graph. The target relative humidity is 22.5%{saturated}, which will, together with the inlet temperature and the ambient specific humidity, give a product temperature of 42.3°C. We also can see the product temperature that will give a saturated condition, 24.8°C. The relative humidity based on the product temperature is 15.9%{saturated} and the outlet relative humidity is 22.9%{saturated}. The relative humidity created by the spraying is 24.1%{saturated}.

Finally, the lower left corner shows general process information, such as the time that has elapsed, the amount of solution delivered to the process and the current rate of spraying and process gas volume flow rate.

The product transport pressure is measured as the pressure difference between the empty equipment at the given volume flow rate and the current pressure loss over the equipment. With this value, it is possible to calculate how much product is moving around in the equipment, using the first law of thermodynamics, the conservation of enthalpy.

References

1. Ebey, G.C., "A Thermodynamic Model for Aqueous Film-Coating," *Pharmaceutical Technology*, (1987), April.
2. Okhamafe, A. O., and York, P.," Characterization of Moisture Interaction in Some Aequeous-Based Tablet Coating Formulations," *Journal of Pharmacy and Pharmacology*, (1985), pp. 37, 385-390.
3. Hyland, M., and Naunapper, D., Process Development Group, Goedecke, A.G., and Glatt, "Continuous Control of Product Moisture Content in Drying Process, Drug made in Germany," (1988), No. 1, p. 31.
4. Wantano, S., Hiroko, T., et. al, "Modeling Drug Release from Granule Coated with an Aequous-Based System of Acrylate Methacrylate: Effect of Moisture Content on the Kinetics of Drug Release," *Chemical Pharmaceutical Bul-*

letin, (1994), 42(11) 2338-2341.
5. Watano, S., Kiyomi, Y., et al., "Evaluation of Aequous Enteric Coated Granules Prepared by Moisture Control Method in Tumbling Fluidized Bed Process," *Chemical Pharmaceutical Bulletin,* (1994), 42(3).
6. Watano, S., Ikuko, W., et al., "Modeling and Simulation of Drug Release from Granule Coated with Aequous-Based System of Acrylic Copolymer," *Chemical Pharmaceutical Bulletin,* (1995), 43(5).
7. Walter, K., "Real Time Process Determination to Achieve Reproducible Coating Results," Proceedings Second European Coating Symposium, (1997), 227-235.
8. Walter, K., "A New Method of Controlling the Process Humidity when Coating Particulars," Proceedings Fifth European Coating Symposium, (2003), 82-87.
9. Larsen, C. C., Holm, P., et. al., "A New Process Control Strategy for Aqueous Film Coating of Pellets in Fluidized Bed," *European Journal of Pharmaceutical Sciences*, (2003), 20, 273-283.

Note: Real Time Process Determination is a trademark of Niro Inc.

About the Author

Kim Walter acquired a Bachelors degree in machine-engineering in 1968. After serving in the Danish Royal Air Force, he earned a Masters degree in machine-engineering and a PhD from the Department of Fluid Mechanics at the Technical University of Denmark in Copenhagen, (former DTH). Throughout his career, he has combined inventiveness and computer programming, beginning with his first invention in noise control and a PhD project that developed a calculation to determine flow around blunt objects using a laser doppler anemometer. He has been with GEA Niro since 1978, beginning as scientist/researcher at Niro Atomizer A/S in Copenhagen, where he worked on kiln technology and patented a new kiln design. In 1991, he became a senior technical advisor responsible for process equipment for the pharmaceutical industry, designing and patenting new equipment - precision coater, roto-processor, precision granulator, and tablet coater. He also developed a new control philosophy, real time process determination, commercially used since 2001. He is now a Senior Process Engineer at Niro Inc., USA, where he is an expert in coating technique and equipment, developing sophisticated and proprietary process technology and building up a technology center used by GEA Niro worldwide. He has numerous patents and published articles. He can be contacted by e-mail at: kw@niroinc.com.

Niro Pharma Systems, 9165 Rumsey Rd., Columbia, Maryland 21045.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Cost and Benefit Analysis of Validation Strategies

by Kent Lohrey

This article evaluates the time (labor effort) required to validate computer or software systems as a function of the applied validation strategy.

Introduction

Each additional day in the marketplace of patent protected sales for a pharmaceutical product or medical device can have significant revenue impact for a company, sometimes on the order of millions or tens of millions of dollars per day. While the duration of patent protection is clearly defined, the portion of that time period where a product is available for sale or generating revenue is variable. One factor influencing how soon a product can reach the market place (or how long the patent protected sales period lasts) is the time spent in development, deployment, and validation of any computer or software system required to produce the pharmaceutical or medical product or the clinical trial supplies required to get the product to the point where it can be sold. Some production lines also require new technologies and computer systems once product sales have started. Increasing product demand can require additional production capacity, which can drive changes to the manufacturing systems. As a result, there is significant pressure on the delivery of new computer or software systems that support or provide the capability to deliver these revenue-creating products. Regardless of business pressures,

Table A. Protocol details by customer, project, protocol, and strategy, including system type and total test items per protocol.

Customer	Project	Protocol	Type of System	Always (ALW)	Only When Different (OWD)
A	1	1	extrusion	1760	
		2	extrusion	916	
		3	compounding	932	
B	1	1	building management/room monitoring	1761	
C	1	1	process analytical technology	554	
		2	process analytical technology	2694	
		3	process analytical technology	1270	
		4	process analytical technology	527	
D	1	1	building management/room monitoring	1444	
E	1	1	building management/room monitoring	2634	
F	1	1	solution preparation/tablet coating		6304
	2	1	solution preparation/tablet coating		5171
	3	1	solution preparation/tablet coating		7076
	4	1	cream production		3521
	5	1	solution preparation/tablet coating		7486
	6	1	building management/room monitoring		2533
	7	1	purified water production and distribution		1176
G	1	1	Chromatography		1008
7 total	13 total	18 total	Average:	1449	4284

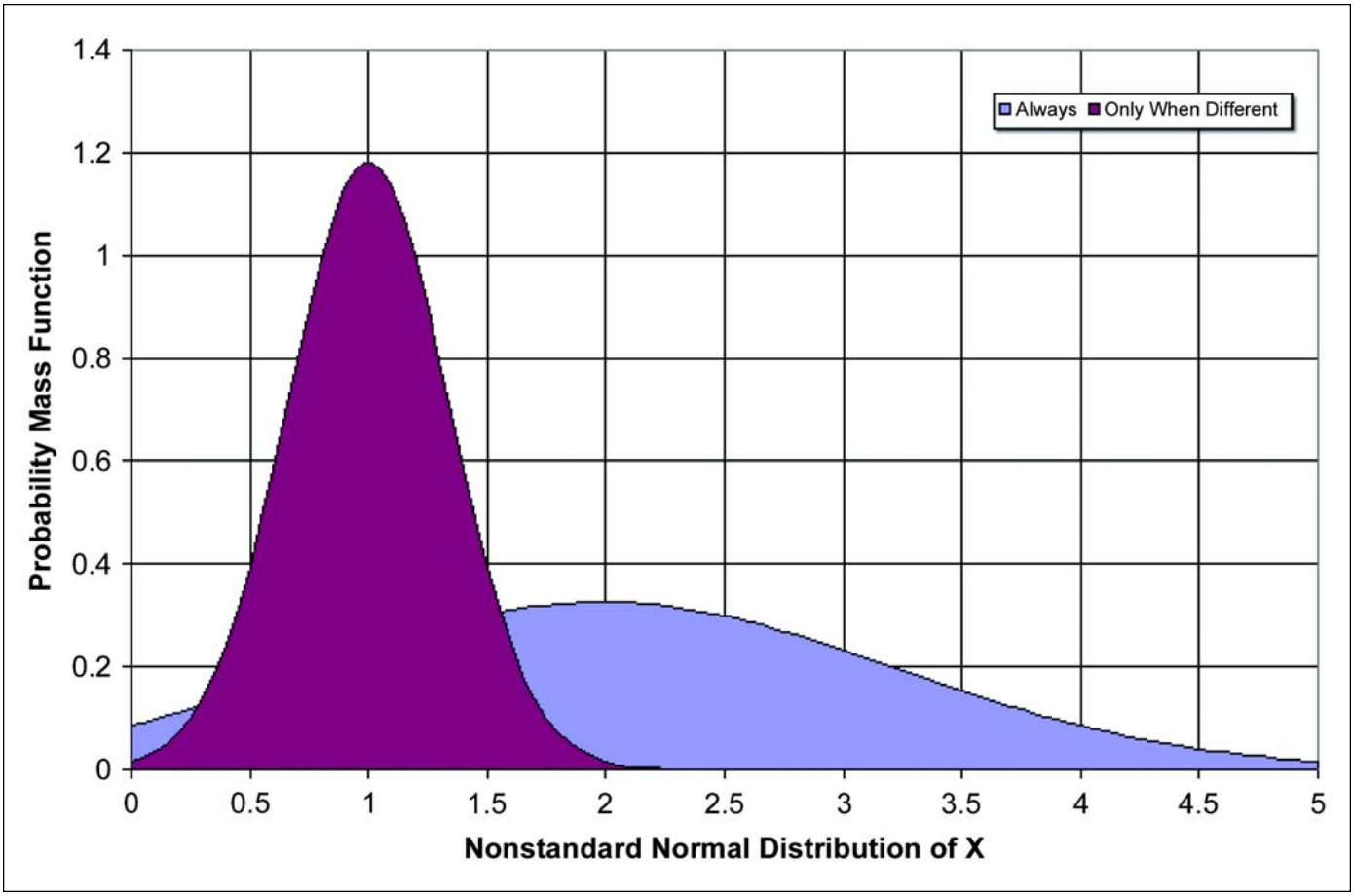


Figure 1. Normal distribution of scaled data (scaled OWD mean = 1.00, scaled ALW mean = 1.99).

these systems also must be deployed in a manner satisfying all applicable regulatory requirements, including software validation.

Companies have chosen to apply different validation strategies that are conducive to rapidly delivered and regulatory compliant systems. This article evaluates the time (labor effort) required to validate these computer or software systems as a function of the applied validation strategy. This is accomplished by comparing testing metrics collected from the execution of many protocols on several system validation projects where different strategies were applied by different companies. Analysis of this data quantifies the impact of the differing strategies. Advantages and disadvantages of each strategy are discussed in the context of regulatory requirements, and some conclusions are suggested to consider when setting validation strategy for future projects.

All of these validated systems controlled FDA regulated activities for pharmaceutical or medical device manufacturers. Most of the systems were manufacturing control systems (e.g., extrusion, Process Analytical Technology (PAT), solution preparation, and tablet coating). The remaining systems included building management systems, room monitoring systems, and purified water production and distribution. All of these systems were delivered for items already in production except for the PAT system which was used to produce clinical trial supplies.

Data

Data from validation test execution has been collected for a variety of purposes, including evaluating project or task efficiency and estimating future work. This data also can be used to compare validation strategies applied by different companies, as each company has its own method to satisfy the regulatory requirements for system validation, while attempting to meet business needs.

The data includes the cost of testing time in units of hours. This eliminates influences on the data, and the corresponding conclusions, due to different rates or hourly charges related to resources on different projects. Time is an acceptable unit for comparing different validation strategies as testing cost in dollars is directly proportional to testing time, meaning that an increase in time will create an increase in costs.

Test execution is quantified by calculating the average number of hours used to execute each test item or testing time per test item. This calculation requires dividing the total hours used to execute a test protocol by the total number of test items within the protocol. The test execution time includes all of the following tasks: creating test conditions, observing results, assessing the results (pass or fail), documenting actual results, writing deviations (test discrepancies), and implementing the resolutions defined within deviations. Deviations include specification changes, protocol

changes, system changes, and retesting or additional testing required.

The data used in this analysis are from 18 separate test protocols executed as part of 13 control and information system projects where hardware and software elements of a system were validated. These projects were performed with a total of seven different companies. Table A includes important project and protocol attributes for the data. Common elements of all of these validation studies included:

- protocols developed to be consistent with **Good Automated Manufacturing Practice** (GAMP4) principles
- cGMP documentation rules in effect
- structured protocols derived from the validation company (contractor) test template
- clearly defined and consistent test instructions and acceptance criteria (for example, in some cases, the exact same user interface test instruction language was used for different protocols with different customers)
- pass or fail assessment made for each test item
- deviations required for specification, system (hardware or software), or protocol changes that are needed to address failed test items

Significant differences were present in the validation strategies employed. These differences surrounded two fundamental choices in the strategies used, when to document actual results and when to use a risk-based approach to testing.

Two different actual results strategies were used on these protocols:

- actual results recorded at all times (five companies, 10 protocols), referred to from this point on as ALW for the Always recorded strategy
- actual results recorded only when the actual results were different than expected (two companies, eight protocols), referred to from this point on as OWD for Only When Different strategy

Two different risk strategies were used on these protocols:

- testing 100 percent of design specification content (five companies, 12 protocols) or
- applying a risk-based (less than 100 percent) test approach (two companies, six projects, and six protocols)

The same set of companies, projects, and protocols was used to analyze both major strategies. Individual companies consistently used the same actual results strategy for all of their projects. Some of the companies applied only one of the risk-based validation strategies, while others used both risk-based strategies depending on the specific system and project. Each strategy is addressed separately below.

All test execution time included in this analysis was expended by either contractor employees or employees from the customer companies. The total test execution time for each protocol was obtained from a combination of time sheets and test activity reports. All contractor time was documented on time sheets reporting testing hours on a daily basis. The hours reported on these contractor time sheets also were submitted to and approved by the customer companies through approval of a daily activity report. This approval step and a customer's financial incentive to only pay for work performed ensured accuracy in this time sheet data. The daily activity reports, generated by the contractor, also documented when customer employees assisted with test execution activities as defined above. The accuracy of this total test time component is robust, but not as robust as the time sheet data because these reports were based on contractor observations, not direct input from the customer employees. As a result, some inaccuracy is possible in the customer time contribution to the total time. The extent of this possible inaccuracy is unknown, but mitigated by the following:

	Always (ALW)	Only When Different (OWD)
Count of Protocols	10	8
Mean	1.99	1.00
Standard Deviation	1.22	0.34
Minimum	0.91	0.61
Maximum	4.60	1.59

Table B. Scaled data comparing testing time impact of actual results strategies (values divided by OWD mean).

- Only eight of the 18 protocols included customer time. On these protocols, the customer time averaged less than one third of the total time spent on a protocol.
- The contractor employees were responsible for coordinating all test activities, regardless of who performed them.
- Most of the customer contribution was performed in combination with the contractor employees or performed independently, but in the same room as the contractor and when the contractor was present.

Validation Strategy: Actual Results Documentation

Data

The actual results data analysis produced a mean test execution time per test item metric and a standard deviation for the protocols within each strategy. The units for these values are hours/item. Dividing the mean and standard deviation from each population by the mean for the OWD population scaled the data, changing the values from hours/item to a percentage of the mean for the OWD population. For example, the OWD mean value scaled results in a value of 1.00 (the mean divided by itself). The mean for the ALW population is 199% of the OWD mean, reported as a value of 1.99 in Table B (ALW mean divided by OWD mean = 1.99). Comparison of the scaled test time per test item for the ALW and OWD populations shows the ALW method requires double the execution time per test item, compared to the OWD method.

The scaled mean and standard deviation results are represented in Table B. Table B also includes the scaled mini-

mum and maximum test execution time per test item values found within each population.

The scaled test time per test item results are presented in Figure 1. This figure uses a normal distribution of the data shown in Table B to illustrate the difference between the two populations. Not only was the ALW mean much greater than the OWD mean, but the standard deviation also was much greater (scaled value of 1.22 compared to 0.34 or approximately 3.6 times greater). This shows the execution time for the ALW tests was far more variable than the OWD tests. Stated another way, the mean test time per test item in the OWD population was much more consistent. It is likely that the ALW population variability was driven primarily by differences in the types of actual results required within the ALW population. For example, some ALW tests only required printing and referencing a screen capture, which requires much less time to document than re-writing the entire set of expected results in the protocol as was required for some of the other ALW tests.

Strategy Comparison

The different actual results strategies have important similarities and differences. The differences create advantages and disadvantages for each strategy as summarized in Table C.

Applicable Regulatory Requirements or Guidance

Current Good Manufacturing Practice (cGMP) requirements are defined in 21CFR Part 820. These requirements include at least two references to the results of validation activities. The regulation for production and process controls defines a requirement for results documentation during validation of automated processes as follows: "*Automated processes.* When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented."[1]

Similarly, the cGMP regulation for process validation defines the requirement for results documentation within process validation as follows: "The validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be documented."[2]

These requirements call for documentation of validation results. The requirements do not specify instructions for application of these requirements or if these results requirements apply specifically to actual test results. Therefore, individual companies must interpret the requirements and decide how the requirements can, or should, be implemented. The number of companies and protocols within the data analyzed in this article is only a small portion of the pharmaceutical and medical device industries. However, these companies do offer some insight into how regulated companies have attempted to implement validation strategies to address this result requirement.

The companies choosing the ALW method often explained this choice as being based on the presence of actual

	Always (ALW)	Only When Different (OWD)
Similarities	• Testing is the same: test instructions, initial conditions, and expected results • Does not take varying priorities of tests into account • Relies on the integrity of the personnel involved	
Differences	• Every test requires the tester to document actual results	• The tester is only required to document actual results when they differ from expected results
Advantages	• Evidence of actual results is provided for every test • Reviewers (including auditors) have more insight into test results • Availability of evidence may eliminate need for witness to testing • Can include some objective evidence (such as screen prints or reports) for every test of a specific type	• Evidence is collected and documented when dictated by actual results (as part of a deviation) • Less time is spent recording actual results, requiring less time and cost (labor, either internal or vendor) • Less documentation requires less time by reviewers
Disadvantages	• Increases opportunities for human error (such as writing actual results incorrectly) • Some actual results can be generated by more than one set of instructions and conditions and recording only actual results provides no insight into this part of the test • The method of collecting evidence can create issues (for example some companies save screen prints as .jpg files - a format that can be easily edited - the use of electronic files for evidence may constitute use of electronic records to satisfy regulatory requirements, possibly invoking 21CFR Part 11 for these actual results) • More time is spent recording actual results, requiring more time and cost (labor, either internal or vendor) • More documentation requires more time by reviewers • Provides inconsistent levels of evidence when different types of evidence are used (such as written vs. screen prints)	• No objective evidence is collected for successful or passed tests (such as screen prints or reports) so no evidence is available for reviewers or auditors on these tests • May require additional resources for witnessed testing

Table C. Comparison of different actual results strategies.

	100 percent Test	Risk-based
Similarities	• System design included GMP-critical and non-GMP features and functions	
Differences	• All specified design elements are fully tested	• Some specified design elements are fully tested, others are partially tested
Advantages	• System is comprehensively tested creating less risk of even minor issues going unnoticed • No justification needed for testing reductions (less documentation) • Less perceived risk by individual reviewers and approvers	• Reduces execution time and paperwork generated by testing, reducing time, and cost • Risk assessment exercise focuses project and personnel on highest priorities
Disadvantages	• Increases execution time and paperwork generated by testing which increases time and cost • Treats all design features and tests as equal in importance or priority • Can prevent inclusion of some useful features due to associated testing costs	• System is not comprehensively tested, increasing the risk of some issues going unnoticed • Justification needed for testing reductions (additional documentation) • Perceived risk by some reviewers or approvers as they approved the reduction in testing • Requires additional design considerations to support risk strategy • May need additional design work to limit access to non-GMP functions through security (user level) requirements • May need additional design work to create features that are universal and can be reused on different systems (designing to satisfy multiple systems)

Table D. Comparison of different risk strategies.

results, for all tests, generating a higher confidence during internal reviews. These documented results also were cited as a critical component when defending the documentation in any audit activities.

Those applying the OWD method decided documenting that a test passes is the functional equivalent of writing down actual results when the results are the same as expected results. The test performer is documenting the actual results without rewriting them in the protocol by indicating that a test passed. In these protocols a "pass" assessment was defined as the actual results matched the expected results.

Conclusions

Within the limited population used in this analysis, companies more frequently chose the ALW method, by a ratio of 5:2 in this sampling. Validation strategy discussions with the companies using the ALW method revealed a very strong belief that anything less than always documenting actual results for each test was inviting regulatory failure. In many cases, validation personnel called on their experience with past regulatory audits to explain the necessity for their chosen strategy. These experiences hinged on a greater comfort level that auditors had expressed with the actual result documentation provided for every test. These companies did not cite specific regulatory requirements as part of the rationale for choosing the ALW strategy.

Even within the ALW strategy companies, there was varying confidence placed on different types of actual results. Objective forms of results evidence like screen captures or prints generated a much higher level of confidence than the written, subjective observations of a test performer. As noted in Table C, even verifiable objective evidence like screen prints have limitations in the insight or value they can provide to a reviewer. The fact that a screen print cannot provide specific definition of the actions taken to generate the actual result prevents even this objective method of capturing results from providing a faultless illustration of all critical aspects of the test. The chain of evidence used to support a pass or fail assessment on an individual test can only be as strong as the weakest link. If only the test results are documented with evidence, written or otherwise, the unsupported or weak link in the chain of evidence is still relying on the integrity of the tester to have used the instructions and initial conditions provided to generate this documented result. If a company must rely on the tester's integrity for the instruction part of the test, then is it possible or reasonable to rely on the same integrity for the result?

This was a central part of the OWD strategy justification for individuals within the two companies not using the ALW method. Both of these companies believed it was completely reasonable to rely on the tester for the accuracy of both the instruction and result portion of a pass or fail assessment. Both also concluded the regulatory requirements did not necessitate documenting actual results when the results were a match with the expected results defined in the protocol. Additional results documentation and the associated effort did not provide a significant compliance advantage, in their opinion. However, recording actual results was an obligation on these protocols and provided additional results evidence when the expected results defined in a protocol were not observed. In this scenario, the actual results were documented as a deviation to the protocol. For example, if a valve graphic turned the wrong status color when a valve alarm occurred, the deviation would document the behavior found, any required corrective action (e.g., specification or software change), and any retesting required.

Like the ALW method, the OWD strategy also has disadvantages. Screen prints, and other evidence like reports, can offer objective evidence that can support a test assessment of "pass" in a visual way that can be very powerful. Not using

evidence like this for passing tests denies future reviewers of evidence that could support at least the result portion of the tester's assessment. Reduced evidence for reviewers and auditors is a disadvantage in the OWD method that could offset some of the time and cost savings offered by this method.

Both strategies present disadvantages or challenges that must be carefully considered before choosing a validation strategy. The impact to schedule and cost is significant with the ALW method taking double the test time per test item for test execution. A lack of actual results evidence for passed tests in the OWD method, even for the most critical tests, could invite or influence a future regulatory review.

One possible solution to these challenges is to apply a risk-based approach to the need for actual results. A hybrid strategy could be adopted to require the ALW method for only the highest risk items. This limits cost and schedule impacts of the ALW method, while still providing evidence of actual results for every high-risk test. The OWD method could be applied for non-critical tests. For example, in a system where temperature is a critical process variable, temperature alarms are likely to impact the quality, safety, or efficacy of the product. As a result, these critical alarms deserve a high degree of scrutiny. At the same time, system usability features such as colors displaying device status do not have a direct impact on the product, requiring less emphasis on the verification of these system functions. Using this mixed strategy requires the instructions and acceptance criteria to clearly define where the different actual results methods apply and how they must be implemented. This hybrid and risk-based approach to actual results recognizes that all test items are not equal in terms of the functions or requirements they address while allowing companies to limit the time and cost impacts of validation testing.

Validation Strategy: Risk-Based Testing

Data

The risk-based data analysis focused entirely on those projects that applied some level of reduced testing based on risks evaluated within the system. These projects fit into two distinctly different types of risk-based approaches. In both types, these systems were designed to support the application of a risk-based strategy. Reviewing the specific system design specifications and counting the individual design elements and conditions not tested quantified the amount of reduced testing.

Five of the risk-based protocols applied a strategy of reduced testing for the control system software by minimizing testing of maintenance only functions. The design included some windows containing content only required for maintenance purposes. Access to these windows was restricted to prevent system operators from accessing these functions. These windows also contained no GMP critical information. All GMP critical information and process control was included in other portions of the applications. These restrictions supported an approach to test a representative sample of the functions included in windows like a variable frequency drive status window. Testing 100 percent of these window features would have added on average approximately 13 percent more test items to validation tests that already averaged nearly 6000 test items per protocol.

One of the projects in the data analysis applied a different risk-based strategy. In this project, a control system application was developed for use on a number of different systems that had many common components. This application was designed generically in the windows that were used on each of the systems (such as the security and alarm summary windows). The application was used to control a suite of air extrusion systems. Some were single extruders and others were co-extruders (two extruders). The components of the single extruder were the same as the first or primary extruder in the co-extrusion systems. This allowed the primary extruders and single extruders to be controlled through the exact same set of user interface objects that were designed and programmed the same, except for linking to different field equipment. The design also disabled any window features that did not apply on a specific system. Secondary extruder objects were disabled when the application was installed on a single extruder system.

The first of these systems tested included almost all of the features common to all systems (a co-extruder) and was executed fully. The second installation of this application applied a risk-based approach to testing by not repeating tests of unchanged functions. For example, the access limits defined for a setpoint entry object in the user interface were entirely a function of the user interface objects, not the system attached to the software. These features were not retested. Full testing was limited to features not previously tested and those software components interacting with the specific system devices. This included testing of analog inputs like temperature, line speed, and pressure. Outputs like those related to starting and stopping devices also were tested. The protocol for this second installation included approximately 900 tests. Testing 100 percent of the software features, including those common features, would have required more than 1600 additional tests, an increase of more than 150 percent.

Strategy Comparison

The different risk strategies have important similarities and differences. The differences create advantages and disadvantages for each strategy as summarized in Table D.

Applicable Regulatory Requirements or Guidance

Current Good Manufacturing Practice (cGMP) requirements defined in 21CFR Part 820.70 also apply to this risk-based strategy scenario. Part (i) for automated processes requires companies to "validate computer software for its intended use."[3] This regulation could be interpreted to demand 100 percent testing of all specified software elements as additional language in this section specifically directs validation of all software changes.

The door to the use of a risk-based strategy was opened in

2002 when the FDA announced a new initiative to enhance the pharmaceutical GMP rules and regulations. "The first goal will be to enhance the focus of the Agency's cGMP requirements more squarely on potential risks to public health, by providing additional regulatory attention and agency resources on those aspects of manufacturing that pose the greatest potential risk."[4]

The risk-based strategies used by the projects analyzed actually applied a minimal amount of risk when identifying testing that could be reduced. Risk-based decisions were limited to areas that did not affect electronic records or electronic signatures and software features that did not influence or alter product safety, quality, or efficacy. This avoided the aspects of manufacturing that pose a great degree of potential risk, minimizing the need for FDA scrutiny of these risk-based decisions.

Conclusions

More than half the projects included in this data analysis did not apply a risk-based approach. These companies and projects shared a common element: individuals were more comfortable with the 100 percent testing method. Validation strategy and test protocol approvers perceived risk-based validation as a potential compliance risk. This, in turn, was seen as a personal risk if they were associated with approving a potential compliance risk and a future regulatory activity questioned that choice.

Both of the risk-based approaches applied by the organizations in this sample delivered noticeable time and cost results for the companies. In the case of the maintenance function approach, the applications were able to include helpful monitoring and troubleshooting capabilities with minimal additional testing. These additional features will aid the company during operation and maintenance activities for years to come. Data from these projects demonstrate how risk-based testing allows an increase in application features for the same or less testing time than a 100 percent tested application. These projects could have pursued an even greater savings, beyond the average 13 percent, by applying the risk-based approach to testing of other non-critical features within the applications that were not isolated from critical functions as well as the maintenance functions.

The second risk-based approach, multiple installations of the same application, cut the number of test items by more than 50 percent on the second installation. The software was considered a custom configured application (GAMP category 5) for this company, which typically requires validation of the complete system.[5] Through careful design choices and use of common user interface objects, the company reduced validation testing time and assumed very little compliance risk in the process.

The risk-based method focused these project teams and testing resources on the highest priority aspects of the specific systems which impacted quality, safety, or efficacy of the product. These critical features were fully tested. In these organizations, the project decision-makers were encouraged and supported in the risk-based work.

Those companies applying a risk-based approach were able to validate their systems, while avoiding significant testing time which would have been required by using the 100 percent testing method. This time savings was achieved also while maintaining a strong position for any future compliance reviews through full testing of all critical functions. These projects proved a risk-based approach could provide regulatory compliance and reduce testing time (costs) simultaneously.

Discussion

The different validation strategies discussed above each have advantages and disadvantages. While some strategies may appear to be more commonly accepted, the more commonly used testing strategies – to always document actual results and to apply no risk-based reductions – drive validation testing time and costs up as indicated by this data analysis. Full or limited use of the other emerging strategies can generate schedule and cost benefits that merit consideration by companies needing to design, validate, and deploy systems within their own budgetary environment and regulatory history.

Considering these strategy options and their tangible impact on time and cost is likely to either generate more confidence in the current methods applied by a company or provide ideas for changes to future validation strategies. Regardless of the validation strategy chosen, clearly defining and documenting the strategy applied will provide the basis for validation decisions and support the defense of the applied strategies in any future regulatory compliance evaluations or audits.

References

1. 21 CFR Part 820.70 (i).
2. 21 CFR Part 820.75 (a).
3. 21 CFR Part 820.70 (i).
4. FDA Press Release, "FDA Unveils New Initiative To Enhance Pharmaceutical Good Manufacturing Practices," August 21, 2002
5. *GAMP® 4, Good Automated Manufacturing Practice (GAMP®) Guide for Validation of Automated Systems,* International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001, Appendix M4 - Guideline for Categories of Software and Hardware, p. 4. www.ispe.org.

About the Author

Kent Lohrey attended Princeton University, earning a Bachelor of Science and Engineering (BSE) in mechanical and aerospace engineering (with honors). While at Princeton, he was a cadet in the Air Force Reserve Officer Training Corps and received a commission in the United States Air Force. Following graduation, Lohrey reported to the Space and Missile Center, Los Angeles Air Force Base.

During his time in the Air Force, Lohrey held a variety of positions, including the liquid propulsion engineer for the TitanII and TitanIV launch vehicles where he supported the launch of the Cassini spacecraft mission to Saturn. After the Air Force, he joined Accenture as a process consultant. While at Accenture, he led the design and validation of controlled document management systems for pharmaceutical companies to comply with 21 CFR Part 11 requirements for electronic records and electronic signatures. Lohrey joined the validation department of Total Systems Design (TSD), Inc., a control system integrator, in 2002 and he is currently the Validation Program Manager. In this role, Lohrey sets validation strategy for the company, manages all validation projects, writes and executes validation protocols, and searches for opportunities to improve validation methods or tools. His most significant accomplishment at TSD is successfully developing and deploying a process and tools to automate the creation of test plan content from design specifications. Kent is a member of ISPE and was elected to membership in Sigma Xi, the Scientific Research Society, for his research work as a Princeton undergraduate. He can be contacted by telephone at: +1-610-857-1666 or by e-mail at: kent.lohrey@totalsystemsdesign.com.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

This once aspiring professional basketball player talks about his unconventional career path into the pharmaceutical industry and Forest Laboratories; his experience running company operations and facilities in different parts of the globe; his thoughts on Quality by Design; the therapeutic areas to watch; and the major industry challenges ahead.

PHARMACEUTICAL ENGINEERING Interviews Richard S. Overton, Vice President of Operations and Facilities, Forest Laboratories

by Gloria Hall, Editor, *Pharmaceutical Engineering*

Long-time ISPE supporters, Rick and Cara Overton.

Born in 1947 and raised in the Naugatuck Valley of Connecticut, Rick Overton came to Long Island in 1977 from Miles (now Bayer) Laboratories to run operations for Forest Laboratories in Nassau County. He holds business management degrees from the University of New Haven and Excelsior College, but was thrust into the area of building design, facilities and equipment acquisition, construction and maintenance when a void occured in the company's engineering staff. Since that time, he has been instrumental in the development of Forest's facility expansion philosophy as the company emerged from its $3 million roots in Inwood, New York to become a $3+billion multinational corporation today. He currently oversees Forest's Supply Chain Team as well as their Long Island, New York operations. He is one of the 26 charter members of ISPE and serves as Vice Chairman on the Board of Directors of the Farmingdale State College Foundation in addition to numerous non-profit organizations.

Q What is your educational background?

A Oddly, I may be one of the only charter members of ISPE who was not an engineer. My education is in business with an AS from the University of New Haven and a BS from Excelsior College. In 1980, I was fully overwhelmed in running the construction and maintenance of Forest Laboratories' facilities. Our fledgling company didn't have any engineers on staff at the time. Most probably because I had worked as a janitor and handyman during summer school breaks in my youth, our CEO, Howard Solomon, considered me as most qualified to take on the task. When I was approached about joining an organization devoted to the advancement of pharmaceutical engineering, I jumped at the opportunity to communicate with others who, I later found, were suffering through the same uncertainties of creating an adequate environment to meet FDA guidance as was I. Since that time, I've become reasonably proficient in the pharmaceutical building trades thanks to my association with ISPE and its terrific membership and professional staff.

Q What lead you into a career in pharmaceutical manufacturing? What experiences and training best prepared you for your current position?

A Maybe I can answer both questions at once. I never anticipated that I would have a career in pharmaceuticals. I fully expected to be a professional basketball player or musician when I left high school, but once reality set in during my early college days, I found myself a dropout, working for Pratt and Whitney Aircraft doing everything from mail

room duty to stationery supplies, to truck driver, to timekeeper, to paymaster, to inventory analyst, to production planner, plus a few other odd jobs along the way. I realized at that point that to advance further, going back to school nights to obtain a degree was a must. That led me to another reality. I needed to make more money. It was at this point that a friend told me of a job opening at the Dome Laboratories, a division of Miles (later Bayer) Laboratories, in production planning. They were about to move to a new facility in West Haven, Connecticut from Manhattan and were looking for new faces. This was in 1969. It was there, in the development of that site, that I cut my teeth in pharmaceutical production from OTCs to oral solid dosage forms to liquids, creams and ointments, to sterile products and beyond, became a supervisor and eventually became a technical advisor and moved into sales, both inside and out.

At about that time, around 1977, I got an offer to join Forest Laboratories as their operations manager as they were moving from Elizabeth, New Jersey to a new manufacturing site in Inwood, New York near Kennedy Airport. Starting at the ground floor inside of a new company better fit my introverted personality than accepting rejection as a detail man in Miles' Boston sales territory so I accepted the position. As a startup, I was forced to learn every aspect of the business from the ground up. Not only was I running operations, but manufacturing and packing orders to collecting money and loading trucks. That is when I drew the short straw and took over the maintenance of the facilities. Over the years, I moved to Puerto Rico to build and run those businesses as plant manager, then returned to New York to help upgrade and construct a couple of million square feet of pharmaceutical floor space, including operations in the US and overseas, primarily in the UK and Ireland.

Q What are the primary responsibilities of your current position?

A Today, I am the Vice President of Operations and Facilities and have direct responsibilities for running our Long Island operations and oversight for Forest's global supply chain.

Q You've been with the company since the late 1970s, watching it grow from a small laboratory service firm that helped larger pharmaceutical companies create new drugs to a major pharmaceutical giant that develops, manufactures, and sells name-brand, generic, and over-the-counter products. What do you think were your major contributions to the company's growth?

A I like to think of myself as a liaison between our corporate environment and our production and maintenance sub-cultures. You might say that I attempt to translate "financial speak" to "production speak."

Q What core philosophies and strategies (the company's and your own) guide your leadership style as VP of Operations and Facilities?

A Forest senior management has always had a strong entrepreneurial spirit and although we have hired employees over the years that are more technically gifted in specific areas than we were, these folks still maintain the ability to think for themselves in creative ways for the betterment of the corporation. I don't think you'll find a Forest executive who won't credit above all else to the strength of our employees as the strength of Forest and its rapid growth.

Q Are there any differences between operations and facilities in Europe and the US? If so, what are they and how do you approach/handle these differences?

A First, let me talk about facilities. Our Irish solid dosage manufacturing operation is both a GMP and EU compliant facility, while our US based operations are mostly built around FDA guidelines. That said, we see more harmonization between agencies than ever before and have tried, through my office, to communicate a consistent approach to building design at each site so that it would be difficult to tell the difference between, for instance, walking into our Irish manufacturing facilities or those at our Cincinnati, Ohio site in the US. They both will be clean, neat, and compliant and although we use local building materials and meet local building codes to take advantage of cost savings, they both will appear similar to the untrained eye. We use the ISPE/FDA Baseline Guides religiously and they have been an enormous help in maintaining consistency.

Our operations have shifted focus over the last 10 years from a series of subsidiary silos producing independently, to a globally integrated supply chain. This came about by a mid-1980s decision to move our primary manufacturing for oral solid dosage forms by the mid-1990s to Ireland to leverage a tax advantage there as well as to have a European base of operations that could more easily integrate with our partner, Lundbeck AG of Denmark for the production of our first blockbuster product, Celexa, an SSRI to fight depression. We chose to ship bulk from Ireland to our Commack, New York and Cincinnati, Ohio packaging facilities that in turn would ship finished goods to our St. Louis, Missouri distribution center to serve the US wholesale market. Communication here is through a network of collaborative site managers who work together on our supply chain team through regularly scheduled conference calls and meetings. We've found that our Informatics (IT) group has been a key component in keeping our lines of communication fluid.

Q What are some of the key metrics used in your organization to gauge operations and facilities performance or success?

A Profit and compliance, not necessarily in that order. Our mission as a supply chain is "to collaboratively ensure the supply of quality products at the right time, place, price, and quantity to fulfill the needs of our customers." With our eye on this bigger picture, each site and subsidiary is tasked with developing their own measurements for throughput, inventory control, and operating efficiency al-

"Our operations have shifted focus over the last 10 years from a series of subsidiary silos producing independently, to a globally integrated supply chain."

though our new President and Chief Operating Officer, Dr. Larry Olanoff, has been instrumental in globalizing certain KPIs.

Q How is Forest increasing efficiencies and product quality? What kinds of technologies are being employed to accomplish this? Is the company embracing the Quality by Design approach? If so, how exactly?

A One of our goals is to seamlessly meld our production and quality groups. Their joint goals and objectives are being coordinated locally and globally. For example, we historically hold a Quality Congress as well as a Supply Chain Team Annual Meeting to bring together all our key directors. In the past, they were held at separate times of the year and there was always the chance that a single message was not delivered by management to both teams. In January, we completed a joint SCT/QA global meeting in which there were independent breakouts for goal setting, but a single shared vision and a final coordinated meeting of the minds on actions for the coming year and beyond without borders. Similar work is being done within our Forest Research Institute for new products as well. Quality by Design is being embraced, but is still a work in progress as you might expect. Our R&D new product development staff are spearheading this, MEP, and PAT initiatives, like NIR, so that our next pipeline products come to fruition using the latest technology that has been proven robust from product inception. Upgrading our training programs for key manager development and to expose more employees to continuous improvement concepts and tools are underway and have been for some time, but in this area as well as in cGMP and SOP training, our concentration is on training for effectiveness and coordinating first time right as a function of not only quality, but personal performance reviews. In the area of measurement, our IT tools like SAP are being reexamined for reports that are more meaningful to the average user as well as the seasoned specialist.

Q What are some of the concerns or issues you have today in your operations?

A As I said earlier, training, staff development, and succession planning are always paramount for employees. Risk management as a business and quality issue is a challenge especially when the company is in a dynamic change to globalization.

Q What therapeutic areas do you see making the most news headlines in the next five years? How do you see Forest being included in those headlines?

A The biotech industry is coming up with new chemical entities daily so what I think is a big deal today may become old news tomorrow, but two areas that come to mind immediately are diabetes and the antibiotic markets. Diabetes delivery systems for the variety of therapies already available may make the first news and most companies are poised to jump in. However, we are more likely, through the recent acquisition of the research company Cerexa in California, to forge ahead with new antibiotics as we see this as a constantly growing and changing market both now and in the future. Of course, our primary corporate focus has and continues to be in the area of CNS, including pain and cardiovascular medications. Forest has a reputation as a nimble company, capable of rapidly responding to a changing environment, like traditional pharmaceutical API licenses moving to biopharmaceuticals so who knows what or where the next opportunity will be? Our corporation was built on our ability to license and develop drugs for the US market efficiently in effective partnerships with primary research companies who are less capable than Forest in understanding how to do the "D" in R&D and weave through the maze of the FDA's clinical and NDA process. Thus, I anticipate that we will continue to fill our pipeline through these partnerships in whatever therapeutic area that presents us with an opportunity to succeed.

Q What technological and operational breakthroughs do you anticipate within the next five years? What do you see as some of the emerging technologies in the pharmaceutical manufacturing industry?

A NIR as well as other PAT initiatives will start to pay off. More companies are likely to use MES as the industry moves away from a paper base. Certainly, rapid release technology is on the rise in drug development and separation technology for more purified APIs so impurities profiles are improved from the get go are here. QbD will enhance this effort overall as it will point out inefficiencies and ineffectiveness early in development.

Q What do you see as the key attributes and qualities in facility design? What do you envision the pharmaceutical facility of the future to look like, say in 20 years?

A Designers are starting to understand the principles of KISS (Keep It Simple Stupid!). Better use of materials of construction for seamless interiors, cleaner details for penetrations, simpler MEP systems that are more self contained and most importantly, miniaturization of equipment environments and enclosures to condition product away from personnel and room structures so that the cost of

operating a facility can be put back under control. We are no longer in a world where a facility can run inefficiently or environmentally out of control no matter where it is located. We can't assume that monster creations that are monuments to a designer or engineer's overkill can just be written off as an overhead that gets built into the cost of goods. Newer facilities must be green, efficient, and effective, as well as be a pleasant place with which to attract employees.

Q What is your involvement with ISPE? When did you first encounter ISPE?

A Today, I have been less active than in the past primarily because of the scope of my daily duties. In the past, I was active on committees, especially for the annual meetings and found the community spirit of the membership has helped me form long standing relationships throughout the pharmaceutical world.

Q What kinds of activities do you enjoy in your spare time?

A I enjoy boating in the summer and skeet shooting in the winter and am active on the board of directors of a number of non-profits and at Farmingdale State College in Farmingdale, New York where I am Vice President of the Farmingdale College Foundation and Chairman of the Finance Committee.

Q In what ways do you believe a global organization such as ISPE can assist regulators, pharmaceutical companies, and individuals in the international arena?

A ISPE for me has been not only an educational resource, but more importantly a clearing house for problem solving and meeting industry movers and shakers. In addition, I've received a wealth of information about equipment and other vendor related support that I might otherwise have approached with skepticism or not investigated at all. Most of all, I've had a lot of FUN in doing so. This is an active group of friends who happen to get together for a single purpose. As a global structure, ISPE has helped and will continue to help expedite the harmonization of pharmaceutical engineering practices which may end up being its greatest legacy.

Q What have been the most significant changes in the industry in the past two decades and how have these changes affected your personal views on the industry's progress?

A The politicizing and ensuing media circus that has developed over drug development and sales has had its pros and cons. I've often thought that if it weren't for those devils in the media, we'd have been able to go our merry way and probably have been stuck in the 1980s technology (and profits) forever. But the world is flat when it comes to our industry today and we must realize that it is overall for the better. We have more competition creating quantum leaps in drug development and improved processes and equipment and organizations like ISPE that help us all keep up to date and moving forward for the good of patients who have the misfortune to need our concoctions, but the good fortune to have us around to supply them.

Q What is your definition of innovation? How does innovation apply to what you do at Forest?

A I may be a bit of an old school hard___, but innovation is nothing more than common sense as applied to the principles of continuous improvement. We've lived by that thinking at Forest and have done reasonably well over the past few years and I believe that it will serve us well into the future.

Q What do you think the major challenges will be for this industry in the future?

A The never ending search for new chemical entities to develop and deliver for the public good at reasonable prices, while maintaining adequate profit to do the research to continue the search might be a concern that we all should think about.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

The Use of Exponentially Weighted Process Statistics (EWPS) and Statistical Process Control (SPC) in High Frequency Data Acquisition of Pharmaceutical Water Systems Instrumentation

The article presents high frequency data acquisition in continuous pharmaceutical processes and illustrates, through the use of EWPS, the need for process understanding, control, and improvement.

by Nissan Cohen

Introduction

Statistical methods for the measurement of process variability are well documented. The greatest proponent of statistical process control was Edward Deming. Although Deming's ideas were often dismissed by the manufacturing sectors of the United States, the Japanese manufacturing industries readily adopted Deming's ideas. Japanese quality in manufacturing surpassed American industries' expertise in the mid 1970s and heralded the beginning of Japanese product dominance in the North American market. Japanese "run-of-the-mill" products were often superior to carefully crafted American-made products.

Measuring changes in the variability of the products produced can identify (and sometimes modify) the characteristics of the process that creates it. Some of the basic tenets of Process Analytical Technology (PAT) are based on this very idea. If the process is measured and understood with multi-variants, then process quality will increase and product deviations will be minimized or non-existent.

A definition of traditional batch oriented pharmaceutical manufacturing can be described as *Discrete Product (DP)* processes or manufacturing processes that produce discrete "products." Discrete product processes produce limited data. DP statistics require that each measurement be independent. This data may be sufficient for the discrete product process, but problems arise when DP statistics are applied to continuous flow production systems.

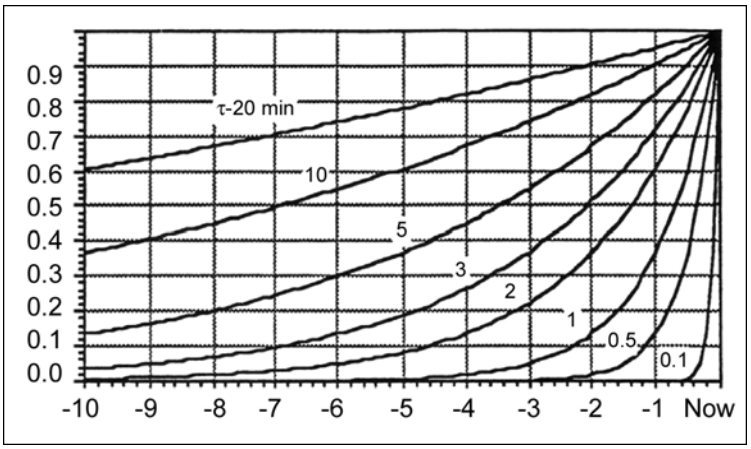


Figure 1. The rate of the weighing function.

Modern pharmaceutical water systems are continuous operations with recirculating flow. The use of on-line instrumentation enhances the monitoring, management, and compliance of the water systems often precluding the need for laboratory off-line testing. Continuous processes with on-line instruments

amass a series of timed individual measurements produced sequentially. Sequential measurements are usually dependent on the preceding one, particularly when a high sampling rate is used. Real-time critical processes require advance warning of an impending upset and typically employ on-line monitoring with alarm generation capabilities. Statistical methods are used to detect subtle process changes.

DP statistics measure the characteristics of a small number of randomly selected samples from the production line and estimate, within known confidence levels, the characteristics of the entire batch. This is known as *statistical inference.*

Continuous processes often monitor process parameters over long periods of time. There is no need to estimate population statistics, as with DP statistics, simply to measure them.

In DP statistics, control chart limits are generally set to ±3s based on the expectation that 99.73% of the samples will fall within these boundaries if the variable is "in control." This leaves only a .27% chance of an excursion beyond these limits. In a continuous process, samples are taken continuously at higher sampling rates than those assumed in DP statistics. The result is much larger sample sizes and a possibility of correspondingly higher frequency of excursions. For example, if frequency measurements are made once each second on a continuous variable, ±3s limits would result in an a probability of an excursion approximately every six minutes as only 99.73% of the readings would comply.

Ultimately, the goal of quantifying and understanding process variability remains unchanged. The methodology by which these statistical techniques are applied must be properly selected to derive the desired results in discrete and continuous processes.

The Use of Statistics

The first and perhaps most useful feature of statistics is the ability to investigate and numerically quantify variations in a measured parameter. If size and variation patterns are established when the process is running well, natural limits may be applied to detect and identify small shifts in the standard pattern. Statistical methods can be used to separate variations due to definable causes rather than random chance. Statistics can be used to isolate and investigate assignable causes. When one parameter appears to be related to another, correlation techniques may be used to quantify the dependency. Often seemingly unrelated parameters can correlate to root causes of deviation.

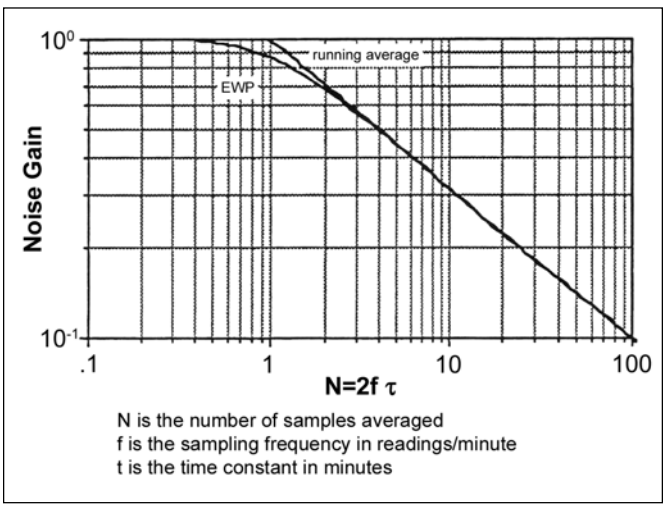


Figure 2. Noise: EWP vs. running average.

Averaging is a common method to depict and track the central tendency of the process. The purpose of averaging or the subgrouping of datums is to reduce the spread in a measurement and track its central tendency. The simplest technique is to average each *n* datums in succession, as shown below. Averaging is commonly used in DP statistics.

Datums	78556	47988	56789	54456	76368	98678
Average	6.2	7.2	7.0	4.8	6.0	7.6

This method has the distinct disadvantage of producing an output only once every *n* readings. If the duration of the averaging period is long, the delay in updates may be unacceptable. A better approach is to use a running average:

Data	**7**	**8**	**5**	**5**	**6**	4	7	9	8	8	5	6	7	8	9	5	4	4	6	5	7	6	3	6	8	9	8	6	7	8
Running Average	**6.2**																													
Data	7	**8**	**5**	**5**	**6**	**4**	7	9	8	8	5	6	7	8	9	5	4	4	6	5	7	6	3	6	8	9	8	6	7	8
Running Average		**5.6**																												
Data	7	8	**5**	**5**	**6**	**4**	**7**	9	8	8	5	6	7	8	9	5	4	4	6	5	7	6	3	6	8	9	8	6	7	8
Running Average			**5.4**																											
Data	7	8	5	**5**	**6**	**4**	**7**	**9**	8	8	5	6	7	8	9	5	4	4	6	5	7	6	3	6	8	9	8	6	7	8
Running Average				**6.2**																										

This method produces an output every reading. A practical limitation with this approach is that each reading in the highlighted running subgroup must be retained in memory and these archiving requirements can become substantial if the subgroup is quite large. Each time a new reading is added to the subgroup, the oldest reading must be dropped. Another shortcoming of both simple and running averages is the lack of any time reference in the calculation of the average. Readings are averaged in the same manner whether they are taken at one second or three day intervals.

In a continuous process, variables average is over a certain time period rather than a certain number of readings. A one-hour average, for instance, may contain three, six, or 3600 readings dependent on the frequency of measurement and could vary from one hour to the next. In relation to monitoring continuous processes, it is the dynamics of the process that dictate the necessary smoothing, not the number of readings. When applying averaging to continuous process measurements, the time periods must be taken into account.

Exponentially Weighted Process Statistics (EWPS)

A technique to solve both problems of time and traditional running averages is to produce a running average based on a time-weighted sum of all previous readings. In continuous processes, the influence of "now" is much greater than a reading in the "past." "Now" has a direct influence on the process. "Past" 30 seconds ago, one minute ago, five minutes ago, one hour ago, and one day ago have a decreasing influence on "now." The purpose of Exponentially Weighted Pro-

cess Statistics (EWPS) is to exponentially weight every measurement and reading. The most recent reading has the greatest influence. As the readings age, their influence wanes. This resolves the issue of equal value for running averages and discrete products. Since each new reading does not require a previous one to be dropped, the weighted sum may be retained in a single register, regardless of the period over which the average is run:

Data	...7 8 5 5 6 4 7 9 8 8 5 6 7 8 9 5 4 4 6 5 7 6 3 6 8 9 8 6 7 8
Running Average	6.2
Data	...7 8 5 5 6 4 7 9 8 8 5 6 7 8 9 5 4 4 6 5 7 6 3 6 8 9 8 6 7 8
Running Average	7.2
Data	...7 8 5 5 6 4 7 9 8 8 5 6 7 8 9 5 4 4 6 5 7 6 3 6 8 9 8 6 7 8
Running Average	7.0
Data	...7 8 5 5 6 4 7 9 8 8 5 6 7 8 9 5 4 4 6 5 7 6 3 6 8 9 8 6 7 8
Running Average	5.8

In this case, each reading must be weighted. The current reading is weighted with a weight of "1" and each prior reading with an exponentially decreasing weight, depending upon the time difference and the selected time constant. If each input is designated as $\mathbf{x_k}$ and each output as $\mathbf{y_k}$.

$$\mathbf{y_k} = \frac{\mathbf{x_k} + e^{-dt}k\text{-}1/t\ \mathbf{x_{k-1}} + e^{-dt}k\text{-}2/t\ \mathbf{x_{k-2}} + e^{-dt}k\text{-}3/t\ \mathbf{x_{k-3}} + \ldots}{\text{sum of the weights}}$$

The weight given each prior reading is of the form $e^{-dt/t}$: where dt is the time prior to the current reading and t is the time constant. The rate at which this weighting function drops off is a function of the selected time constant t, as shown in Figure 1.

$$\mathbf{y_k} = e^{-dt/t}\mathbf{y_{k-1}} + (1 - e^{-dt/t})\mathbf{x_k}$$

This equation is equivalent to the last, but it requires only the current input ($\mathbf{x_k}$) and the last output ($\mathbf{y_{k-1}}$). Thus, only one result has to be retained in memory regardless of the time constant selected.

This function is available for usage in any system to produce exponentially-weighted running averages over any time period. The syntax of the function is:

ewp(*argument*, t, I)

where:

argument = any valid transfer equation argument: a channel name, a raw parameter, or a mathematical expression containing a channel name or parameter

t = the time constant, in minutes

I = The initial value of the function at start-up. (Usually, 0)

As shown in Figure 1, higher frequency of readings has a diminishing influence over time. However, less frequent readings have a great influence over time. The classic example of this phenomenon, in pharmaceutical water systems, is the viable microbial test. Microbial testing is an off-line laboratory test and frequency is commonly once a day or every few days. Based on the results of the test, the pharmaceutical water system is operated on a single datum for the interim until the next test. Thus, the infrequent nature of the testing has an extraordinary influence on the continued operation of the process.

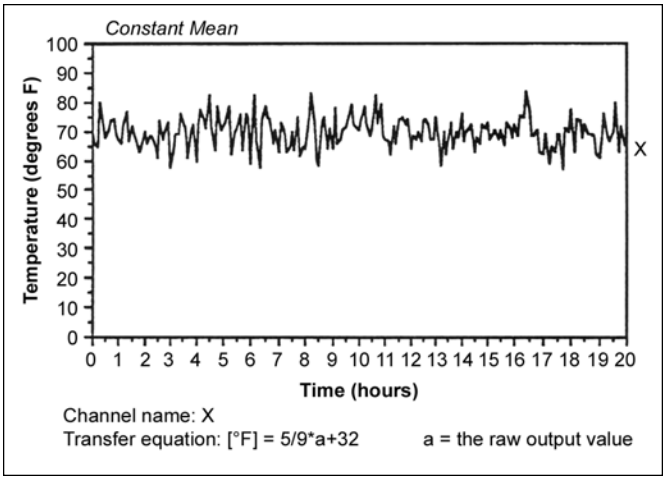


Figure 3. EWPS control chart – Control Chart A.

In DP statistics, it is typical to think and describe in terms of samples and averaging instead of signals and filtering. Although similar in function, the two sets of terms imply substantially different characteristics about the source of the readings. "Samples" is correctly applied to a series of independent measurements if the change in each successive measurement has no relationship to changes in the prior measurement. The example of the microbial testing is of this ilk. Each measurement is independent and has no influence on the successive measurement.

However, in relation to continuous processes, a time series of measurements is constrained by the dynamics of the process itself. If we take the temperature of 5,000 gallon purified water tank at intervals of 1 reading/second, we would not expect the measurement to change or deviate much from reading to reading. Thus, due to the inability of that water volume to change temperature quickly, each successive reading is highly *dependent* on the previous one and the order of reading in the time series becomes essential to the significance of the measurement.

The point of this discussion is to emphasize that continuous process measurements can no longer be viewed as independent samples in the DP sense. The time series of readings must be viewed as a signal, reflecting the dynamics of the process and the effect of the sampling rate. "Averaging N samples" becomes "filtering over a time period." Random variations in the readings can be referred to as "noise." EWP filtering and conventional running averages both average data, but they employ different methods. While conventional running average weights all the readings over the averaging period equally, the EWP filter assigns weights that decrease exponentially with time. EWPS is more responsive to change in the data as the response is twice as fast given the same time increment. This is depicted in Figure 2. The response of the EWPS is faster at the initial start-up. The confluence of both data traces occurs only when the running averages trace has averaged enough data points to conjoin the EWPS response. In fast changing or dynamic environments, the running

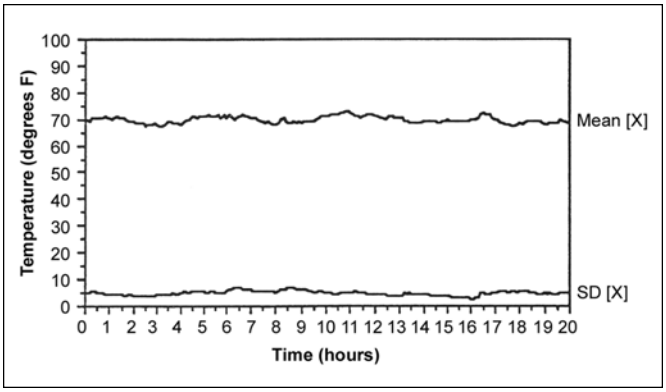


Figure 4. Deriving the population statistic s – Control Chart B.

averages will always lag behind the true changing nature of the process and the EWPS response.

Natural Control Charts

In conventional or DP process statistics, the model for a process variable assumes that the variable is constant and small variations are due solely to random influences. In fact, the purpose of conventional control charts is to detect when this is NOT the case and alert the operator to this condition. This application of statistical methods is of great utility and routinely applied, but it does not address a wide range of process measurements which do not fall into these conditions.

Typical measurements not suited to conventional control charts are process parameters not controlled by the process, but are part of the process. Examples are raw water quality supplied by well water, municipal supplied water affected by seasonal changes, and conductivity. In these cases, a measured parameter may vary in what appears to be random fashion, be affected by another measured parameter, or exhibit cyclic changes with no defined pattern. Typically, the goal of measurement is to quantify the effect the measured parameter has on process quality.

Even tightly controlled process variables exhibit systematic changes in the mean value. For instance, the reaction of a control loop to disturbances in the process is a function of how well the loop is designed, tuned, and maintained. Subtle interactions of two or more controlled variables could upset the consistency of the delivered quality of the water.

No instrument, in a continuous process, always gives the exact same value. The values will deviate slightly from reading to reading even if the actual value is the same, dependent on the sensitivity of the instrument. Subtle changes in the output of the signal can vary slightly in the real process world. Sometimes, this slight deviation is compensated by the use of truncated values.

Using data management software and data acquisition systems, one can construct unlimited variety of process control charts. Examples: real-time update and historical charts of single parameter data, means, standard deviations, +/- 3s calculations with upper and lower control limits, Boolean effects, multiple disciplinary charts with multiple data traces, cause and effect charts with multiple data traces, correlations, etc. A few charts are presented as examples. However, it is the process engineer with specific needs and the ambition to devise analysis methods to solve real-world situations and problems.

To illustrate the value of EWPS and SPC, the following control charts were generated. The first example is Temperature of an ambient pharmaceutical water system controlled at 70°F as denoted in the raw values of X. The control chart of X and the display readings are shown in Figure 3.

In Figure 3, the transfer equation involves simple scaling and offset of the raw measured parameter "a." We have not yet determined what the control limits should be. Control chart limits for individual measurements are calculated in terms of mean and multiples of the standard deviation of the X measurements. The next control charts add the mean and the standard deviation of X.

Mean is denoted by "$\bar{X}$" and produces an on-line average of X using EWP in the transfer equation. By setting the time constant at T_1 long enough, the average is produced over enough readings to represent the population average or the "grand mean" of X as depicted in Figure 4.

Channel Name: $\bar{X}$
Transfer equation: [°F] = EWP([x], 60, 0)

With the 60 minute time interval, the total values displayed at a 1/second frequency are 3600 readings. This chart is labeled as M:X or Mean of X

Channel Name: s
Transfer equation: SQRT(EWP(([X] – [M:X])^2,T,I))

The second displayed channel measures the Standard Deviation of X relative to the $\bar{X}$. Using the same 60 minute constant, t_1, the population statistic s is derived and shown in Figure 4.

The final step in the control charts is to calculate and establish the control limits for both $\bar{X}$ and s. Control limits are set to the mean of the signal +/- n standard deviations of the signal. Not all the data must be displayed to calculate the control limits. Displayed in Figure 5 is the readout of selected data points over 17 hours of readings. The mean of the temperature is 69.754°F and the standard deviation of the

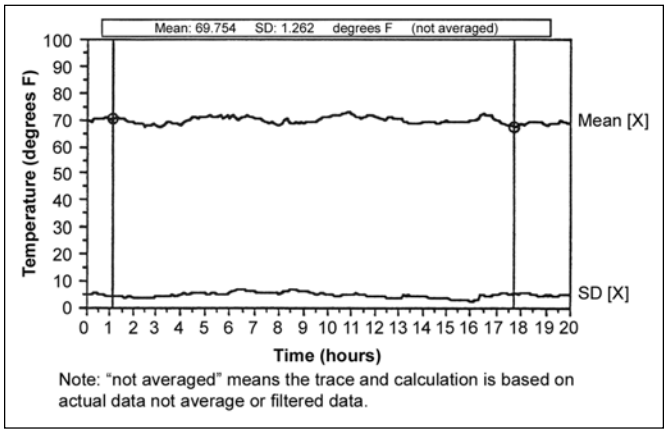


Figure 5. Calculating and establishing control limits for X and s – Control Chart C.

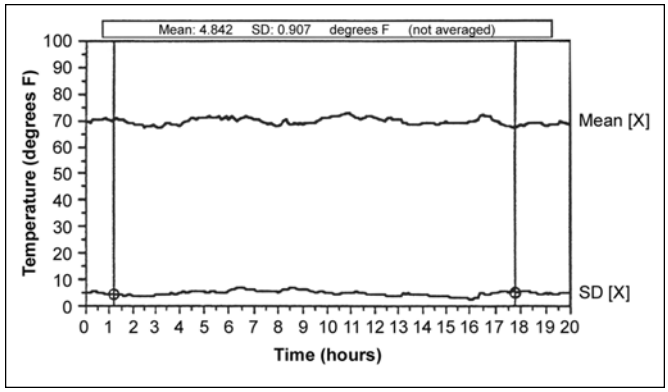


Figure 6. Control Chart D.

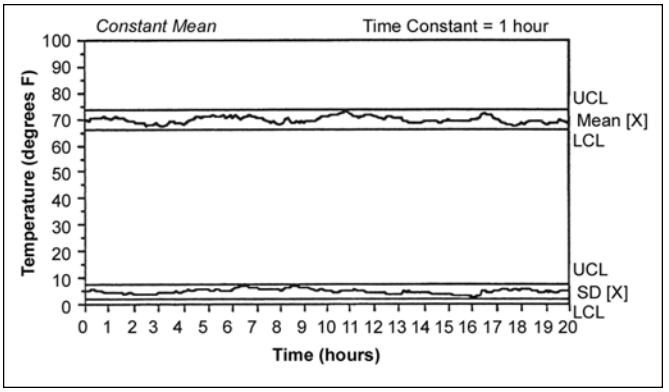


Figure 7. Control Chart E.

mean (X Bar) is 1.262° F. (The trace at the bottom of the chart is Standard Deviation of X, not X Bar)

As seen in Figure 5, the mean of X is 69.754°F and the standard deviation of the mean of X is 1.262°F. If the control limits for the parameter are to be set at +/- 3s, calculations are 69.754 +/- (3*1.262) or 75.53°F as the Upper Control Limit and 65.97°F as the Lower Control Limit - *Figure 7*. However, this 6s spread may or may not be tolerated by the process. Thus, 6s control limits may be too wide for your process and tighter controls may be needed. This is the reason to look intently at the standard deviation and set tight controls on the Standard Deviation data trace.

The Standard Deviation of X is the bottom trace in Figure 6. The mean (X-Bar) of the SD(X) is 4.842 and the standard deviation of the SD(X) trace is 0.907°F (noted as s_s).

Upper Control Limits (UCL) and Lower Control Limits

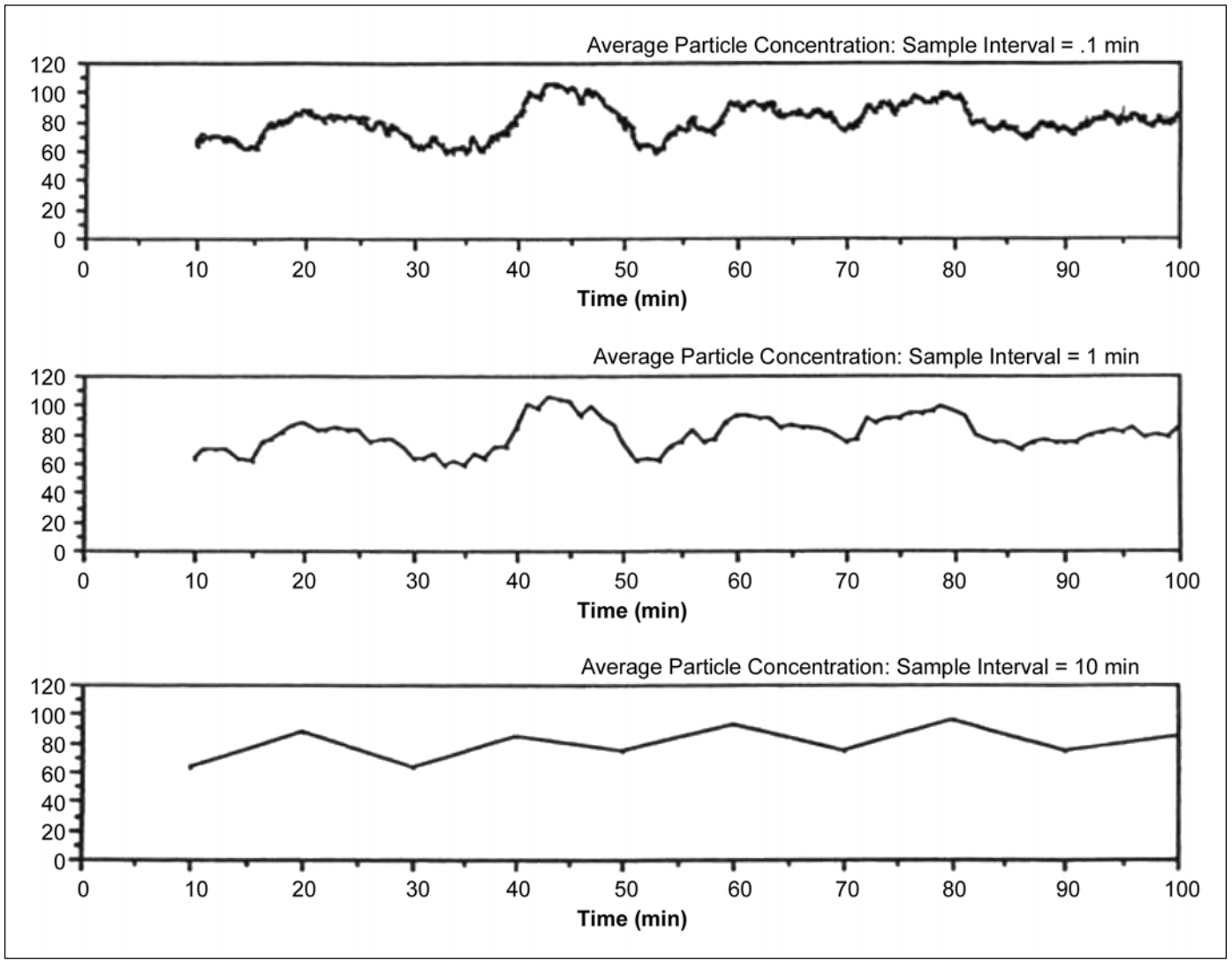


Figure 8. Averaged particle concentration.

(LCL) are calculated based on a +/- 3s or a 6s spread. There are UCLs and LCLs for both the mean value of X and the SD[X] (Standard Deviation). These are calculated as UCL = $\mu_s + ns_s$ and LCL = $\mu_s - ns_s$. In Figure 7, all means, standard deviations, and control limits are displayed.

The control charts depicted illustrate a single value of temperature with a continual trace output. Pharmaceutical water systems have many on-line instruments for the management of the water system not mandated by the USP. Flow, pressure, differential pressure, temperature, and liquid particle counting are not mandated USP measurements, but are important measurements for the stability and operation of the water system. The use of EWPS has a direct correlation on multivariate readings with synergistic influence on the water system.

Example: the start of a pump can initiate a "water hammer" effect, a sudden increase in water pressure affecting various downstream components. The increase in TOC due to sloughage of the filters during a "water hammer" effect is well documented in high purity literature. The increased pressure causes the dislodging of trapped TOC in the filter. The sudden increase in the TOC may cause a spike well above traditional operating levels of less than 100 ppb of TOC. If this spike should register above the 500 ppb (0.5 ppm/L) level, is this considered an action for the immediate shutdown of the water facility or the segregation of the water? The answer is no. The use of EWPS ensures a faster response to immediate changes in the water system without the violation of the protocols and shows the value of the data in short-term, medium term, and long-term operations. If the initial readings were based on a 0.1 minute interval when the spike occurred, then the use of one minute intervals will smooth the value of the spike and render the system within limits. This is not to negate the spike, but the spike can be explained with the data due to the increase in pressure and the start of the pump, thus averting an investigation in the sudden TOC increase. However, the next TOC readings should show a decrease in TOC with a rapid return to the sub-100 ppb level. Without the extensive monitoring and the use of EWPS, the original TOC spike would have never been explained, but relegated to a status of an unexplained anomaly after extensive investigation with no resolve.

Known assignable causes to increases in conductivity: ion exchange exhaustion, R/O membrane breakthrough, small

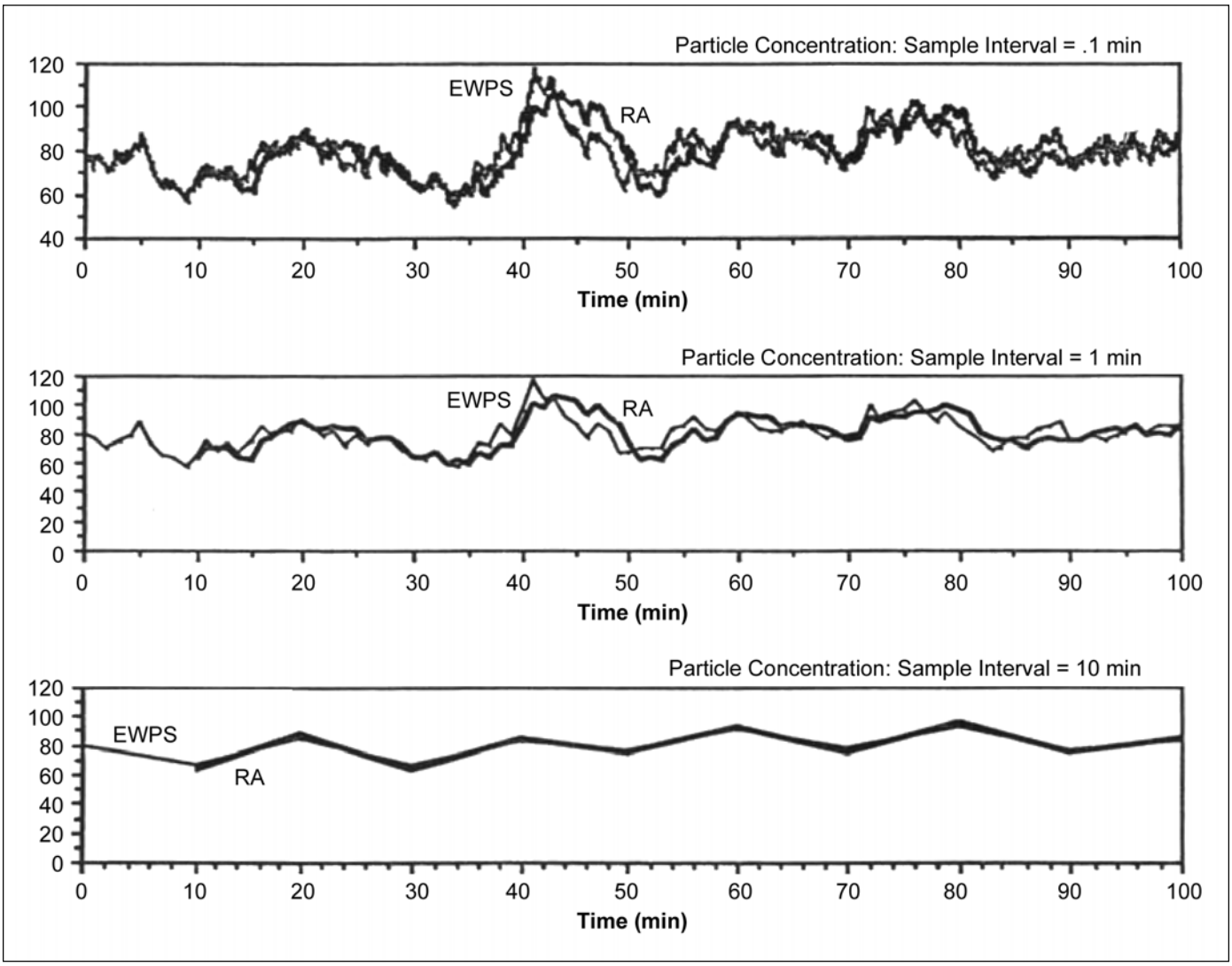


Figure 9. Particle concentration; addition of the EWPS function to the running average data.

molecular weight species of organics partially oxidized to ionic components, atmospheric contamination, etc. With a conductivity measurement alone, how can the various causes of increased conductivity be investigated? The use of data streaming from all of the various water train components can help, but the use of EWPS and SPC charts will notify the operator immediately of a transition above the standard deviation and its limits, depicting whether the spike was an anomaly or is instituting immediate trending toward control limits.

Traditional running averages and averaging programs will not respond quickly to the changing values, especially if long interval averaging is used, as the spike will be smoothed by the next averaging value. The longer the time interval, the less chance of finding spikes in the system. Note the following graphs of a running average of liquid particle counts where the intervals for sampling vary from 0.1 minutes, 1.0 minutes, and 10 minutes - *Figure 8*. Each data set in running average starts at the 10 minute interval increment as a certain number of values is needed for averaging. The increase in sampling interval misses the spikes and smoothes data.

The EWPS response is immediate and faster than running averages for the 0.1 and 1 minute intervals - *Figure 9*. When the interval is increased to 10 minutes the response of each smoothing technique is almost identical with EWPS having an immediate response over the first 10 minute reading interval and running averages initiated only at the 10 minute mark.

Findings and Conclusions

Although this information seems trite, having this data and graphical expression can help monitor and manage the pharmaceutical water system to very tight tolerances with little or no downtime over long periods of time.

The graphical examples shown have been for the temperature and liquid particle counters of a pharmaceutical water system only. Many other on-line sensors, instruments, and devices are installed in a pharmaceutical water system. Signals vary from analytical instrumentation with multi-stream data to singular devices with a single output. The advantage gained is the complete integration of all possible instrumentation into one network, data acquisition, and data archival/retrieval system. Thus, flow, temperature, conductivity, differential pressure, pressure, ozone concentration, TDS, TOC, chlorine, etc. can all be monitored with accurate precision and trending capability.

The purpose of measuring the standard deviation, in real-time, in relation to the actual channeled data from the instrumentation is to enable and understand the reality of the data at any given moment. The use of 6s does not prevent outliers and questions of instrumentation integrity, especially, if data averaging is used. The use of a single standard deviation with tight control limits will inherently alert the user to any deviation which is outside the norm. If an increase in temperature is gradual due to averaging of the data, the system could be out of control long before an alarm is alerted. This statement can be seen in the control charts of the mean. Long averages will cancel out short-term excursions that do not exceed a control parameter. However, the use of tight control limits on the standard deviation trace will depict any reading that exceeds the normal standard deviation. If the standard deviation is .907° F degrees, then anything that exceeds 1.5s of that number can be attributed to a faulty reading or a true trending. If the 6s values of the temperature range from 65-75°F with a mean of 70, a two degree shift is permissible and within the control limits of the process. The issue is how to identify a trend long before a control or specification limit is achieved. The use of EWPS on both the raw data and the standard deviation will alert the user to process issues long before an alarm is tripped.

EWPS can be used on any episodic or analog data stream, for any instrument and any parameter. The exclusive use of 6s for any given process parameter may have too wide a tolerance and may not be indicative of the actual dynamic process parameters.

Continuous processes need accurate data acquisition and management to help determine the dynamic makeup and changes. Although Discrete Products management and its data have been traditional in pharmaceutical manufacturing, the need for continuous data acquisition, on-line trending information, and data analysis as an overall feature of pharmaceutical production processes cannot be overlooked. Continuous processes with dynamic and changing parameters need to be monitored and managed closely to prevent product deviations and quality upsets. Fast and responsive statistical tools like Exponentially Weighted Process Statistics will enable the engineers to assess the issues at hand, take necessary steps, and ensure the process continuity.

References

1. Lucas, J.M., Saccucci, M.S., "Exponentially Weighted Moving Average Control Schemes: Properties and Enhancements," *Technometrics* , (1990), Vol. 32, pp.1-12.

2. Woodall, W.H., Maragah, H. D., "Exponentially Weighted Moving Average Control Schemes: Properties and Enhancements: Discussion," *Technometrics,* February 1990, Vol. 32, No. 1, pp. 17-18.

3. Berthouex, P.M., Wenje, L., and Darjatmoko, A., "A Statistics-Based System for Treatment Plant Operation," *Earth and Environmental Science*, November 1989, Volume 13, Numbers 2-3, 1573-2959 (Online), pp. 247-269.

4. Cox, D.R., "Prediction by Exponentially Weighted Moving Averages and Related Methods," *Journal of the Royal Statistical Society, Ser. B*, (1961), Vol. 23, pp. 414-22.

5. Crowder, S.V., Hamilton, M.D., "An EWMA for Monitoring a Process Standard Deviation," *Journal of Quality Technology*, (1992), Vol. 24, pp.12-21.

6. "EWPS Exponentially Weighted Process Statistics," DataTrax, A Division of Eaton Corporation, Internal Document, (1990), Graphs courtesy of DataTrax.

About the Author

Nissan Cohen has more than 30 years of experience in instrumentation and mission-critical monitoring with emphasis in semiconductor manufacturing, pharmaceutical process and production, ultrapure water, drinking water, waste water, chemical systems, nuclear, hydroelectric, and fossil fuel power generation, and environmental issues of containment and remediation. Cohen has written more than 30 technical and peer reviewed articles for various publications including Pharmaceutical Engineering, Pharmaceutical Technology, Ultrapure Water, Semiconductor International, Contamination, A^2C^2, and The Journal of the Institute for Environmental Sciences. A recognized worldwide expert in TOC and water systems, Cohen is a member of ISPE, the Institute for Environmental Sciences and Technology (IEST), Technical Editor for the Journal of the Institute for Environmental Sciences and Technology, member of the ASTM International E-55 Committee, member of the Pharmaceutical Engineering Committee, Steering Committee member of ISPE Communities of Practice for Critical Utilities, Process Analytical Technology, and HVAC, former Chairman of the ISPE Internet Subcommittee, and Past Chairman of the ISPE Membership Services Committee.

Start-Up Business Development, 267 S. Jefferson Ave., Louisville, Colorado 80027.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Unified Manufacturing Control System (MCS) Architecture for Pharmaceutical and Biotech Manufacturing

by Ronald E. Menéndez and Darrell Tanner

This article reports on a unified MCS architecture using commercially available MES and PCS. It explains the steps in moving beyond paperless functionality to a unified system helping manage information, processes, and people.

Introduction

In recent years, Manufacturing Execution Systems (MES) and Process Control Systems (PCS) have gained wide acceptance in the pharmaceutical and biotech industries, due to the adoption of industry standards and technology advancements. PCS for bulk therapeutic and biotherapeutic manufacturing achieved uniformity in the past decade thanks to the establishment of the ANSI/ISA-88 models for batch control. During the same period, a broader range of industries used MES and ANSI/ISA-95 standards to improve their manufacturing operations.

While MES and PCS found their place in the industry, they were typically viewed as separate solutions within a manufacturing facility. This approach often led to a disparity of systems and organizations responsible for development and maintenance. The resulting systems were usually hindered by a lack of interoperability and dependence on custom interfaces for connectivity.

As companies pursue MES and process au-

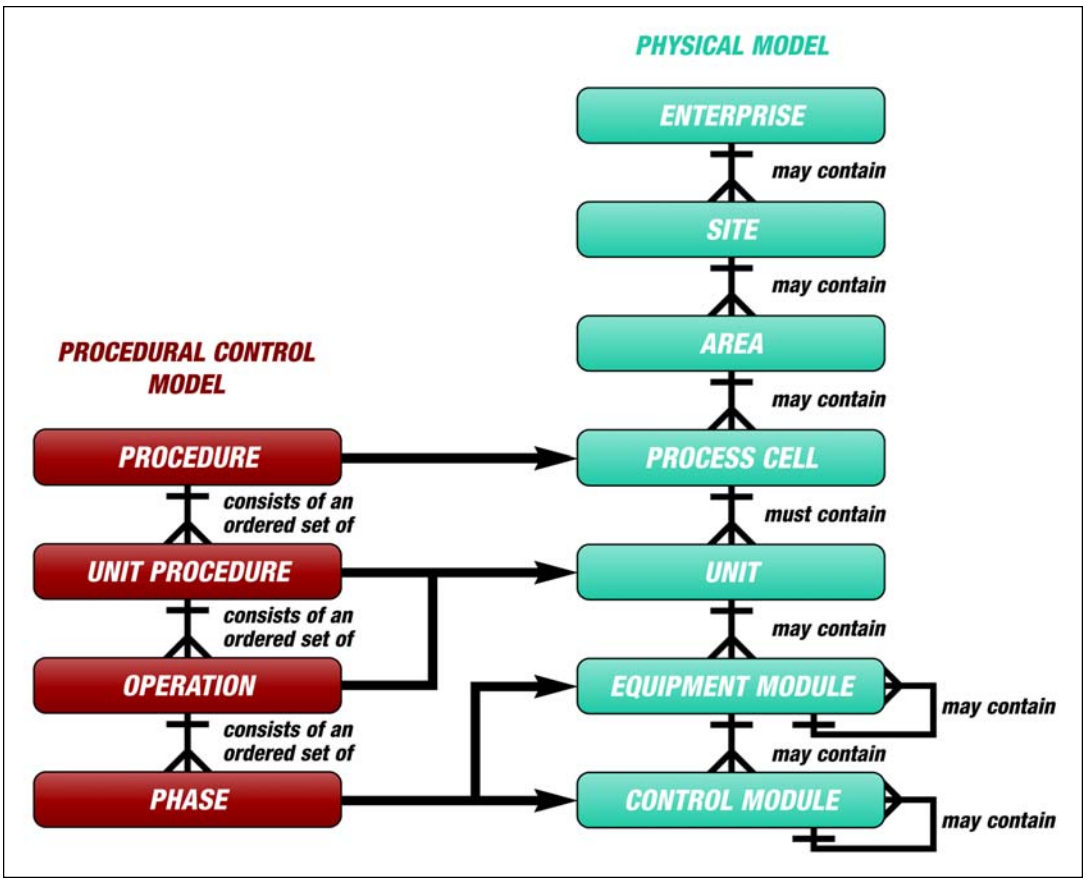


Figure 1. S88 models and methodology overview.

Evolution of Batch Control

A key requirement for effective batch control is collecting useful data and information—and knowing what to do with it. To standardize the use of batch control technology in the process industries, the Instrumentation, Systems, and Automation Society (ISA) established the S88 standard. The ISA guidelines identified a common set of procedures that can be used to describe and define batch manufacturing systems in accordance with U.S. Food and Drug Administration (FDA) current Good Manufacturing Practices (cGMP).

S88 Defines Manufacturing Methodology

The S88 methodology breaks down each manufacturing module into a pyramid of smaller and smaller process steps, known (in descending order) as "procedures," "unit procedures," "operations," and "phases."

The models and terminology incorporated in the S88 standard emphasize good practices for the design and operation of batch manufacturing plants. They can be used to improve control of continuous or discrete processes, and applied regardless of the degree of automation. The standard includes both physical and procedural models that are written once and then employed as templates.

Physical models define the equipment used in the process, such as units, equipment, and control modules, whereas procedural models, which include procedure, operation, and phase modules, define the control enabling the physical models to perform given tasks - *Figure 1*.

Proper implementation of S88 batch automation reduces the time required to reach full production levels for new products. It also helps vendors supply appropriate tools for implementing batch control, and allows users to better identify their needs.

Standard Improves Process Design Philosophy

S88 isn't just a standard for software, equipment, or procedures; it's a way of thinking, a design philosophy. Understanding S88 will help you better design your processes and manufacture your products. Leveraging the knowledge and experience contained in the standard will enable you and your customers to better identify your needs, make recipe development easier, and help reduce the time to reach full production levels with a new system or for each new product. Following the concepts explained in S88, you can improve the reliability of your operations and reduce the automation lifecycle cost of your batch processes, including lowering the initial cost of automating your operations.[2]

tomation initiatives, they are often challenged by varying budgets, schedules, and project methods. That is because automation is traditionally viewed as an engineering discipline, whereas MES is regarded as an IT function. However, in a recent project at a brownfield biotherapeutic manufacturing facility, a new aggregate approach referred to as the Manufacturing Control System (MCS) was put forth as a solution to provide a single environment for manufacturing operations and process automation meeting all requirements of a paperless facility.

This article reports on this system integration effort and presents a unified MCS architecture using commercially available MES and PCS. It further explains the steps in moving beyond paperless functionality to a unified system that helps manage information, processes, and people.

Advancements in Automation Technology

In the 1990s, the advent of open systems in process automation changed the way manufacturers operated their plants. Proprietary computer networks and control applications from automation vendors gave way to PC-based hardware using commercially available operating systems. Ethernet communications employing standard wiring, switches, and routers superseded proprietary communication protocols.

Modern control systems utilizing Web-based Human-Machine Interfaces (HMIs) provide a single, facility-wide view of operations. These systems, designed to integrate business processes with a common HMI across the plant, also provide seamless, third party integration through open Web standards. This trend toward third party integration enabled the advancement of batch control technology benefiting automation end-users throughout the process industries.

Batch Management Increases Flexibility

Batch management software integrated in most PCS available on the market today provides a robust solution for designing, modeling, and automating batch processes. It enables flexible recipe building and management using object-oriented recipe structures aligned with the S88 models. On-line tools allow users to manage multiple batches from the same window, and navigate between displays based on batch execution activities.

S88 batch management applications for automated recipe management and unit procedural control reduce latencies and improve repeatability. This, in turn, improves production efficiency. S88 batch automation ensures procedures are executed in accordance with approved specifications and standard work processes. Using these applications, manufacturers have achieved faster response to production orders and schedule changes, flexible processing to support new product introduction, and increased throughput to meet expanding production demands.[1]

Development of Manufacturing Operations Technology

In a variety of industries, MES has proven to be effective in managing all steps of the production lifecycle; from materials

receipt to product shipment. The technology and S95 standards assist production personnel in managing execution decisions and information during the processes of planning/scheduling down to production execution.

Typical MES provide specification management tools allowing users to define the materials, equipment, and procedures required for production. In many cases, the systems can be expanded to handle multiple production sites - enabling product development departments to quickly deploy new products or update existing product formulations.

Characteristically, MES benefits manufacturers by providing a scalable, Web-based architecture that is easy to deploy and maintain. MES can form the central system for synchronization of business systems with manufacturing and process control - *Figure 2*. Integration with other manufacturing systems can be achieved using Web services and industry standard technologies such as XML and OPC.

Paperless Records Reduce Errors

Key to the adoption of MES technology was its promise of eliminating paper-based batch recordkeeping. With the FDA's re-examination of 21 CFR Part 11 and their issuance of *Guidance for Industry Part 11, Electronic Records; Electronic Signatures – Scope and Application*,[5] there is a greater understanding of the compliance requirements for paperless systems in the regulated industries.

MES makes it easier for pharmaceutical and biologics producers to meet regulatory compliance by managing and recording activities associated with personnel, manufacturing resources, and the process itself. In addition, the MES solution is a direct means to reduced human error during data entry. Users can reduce paperwork, improve overall resource management, and produce fully compliant, paperless production records.

MES provides a "paper-on-glass" replacement for traditional paper formulations, typically referred to as "tickets," by offering prompted data collection, electronic work instructions, and e-signature-based review processes.

Challenges Facing MES Solution

Despite the merits of MES, the technology alone cannot advance the state of biologics and pharmaceutical manufacturing. This is because traditional "paper-on-glass" systems do not collect, organize, and manage all production information - particularly manufacturing and process data generated by the PCS.

Although MES applications have matured around integrated material management and paperless plant-floor operations, which provide significant production efficiencies and cost savings, often personnel find themselves manually managing vast amounts of information. Users are required to refine production data so operations and quality decisions can be made in a timely manner.

Combining today's MES with batch control provides a beneficial architecture for tackling activities such as material tracking/genealogy, barcode scanning, bills of material and work instructions, asset management, lab systems integration, and production dispatching and execution in single, unified environment.

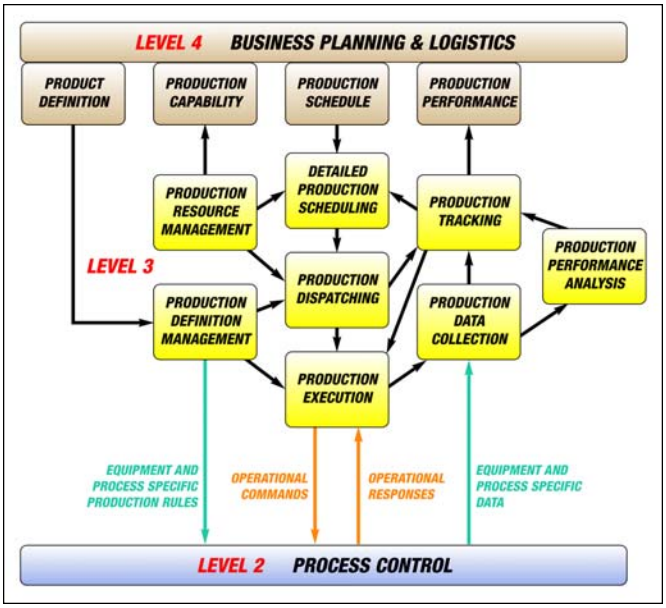


Figure 2. S95 production operations management model.

Benefits of a Unified MCS

The Manufacturing Control System (MCS) is the integration of MES and PCS technology to provide a single solution for production management, process automation, and reporting. This unified MCS design utilizes the strengths of MES for material management and plant floor applications, and at the same time, incorporates the latest advancements in PCS technology - particularly in the areas of automated recipe management and unit procedure control. Together, the two solutions are employed in a way that is most beneficial to operational objectives.

Tight integration of MES and process automation allows pharmaceutical and biotech manufacturers to move beyond "paper-on-glass" functionality and leverage all of the robust capabilities the two systems have to offer. These include: electronic work instruction execution and workflows, material reporting, asset management, laboratory data logging, production dispatching, and Electronic Batch Record (EBR) management.

Open Communications Interface to ERP

Implementation of MCS requires an open, standards-based programming interface allowing communication between MES and ERP solutions and business logic. Such integration enables users to access production-related information from the MES and business applications in real time. This connectivity, made possible by S95 Parts 1 and 2 defining ERP/MES communications standards, is a precursor to MES/PCS unification - and a new level of plantwide integration.

Within the integrated manufacturing architecture, MES serves as an interface to corporate-level 3 and 4 systems, electronic document management systems, laboratory information systems, Material Resource Planning (MRP) sys-

Evolution of MES

In the 1990s, with adoption of the ANSI/S95-95 (S95) standard, manufacturing companies began implementing MES technology to ensure their production operations were capable of delivering on their enterprise's supply chain commitments.

MES holds the potential to significantly improve manufacturing excellence and compliance to regulations. However, realizing this promise requires tight integration of information and work activity across all the real-time levels of the S95 model. Integrated recipe authoring and execution delivers the MES promise across both bulk production and finishing, while reducing the time and risk required to deploy electronic recipes.

Understanding the S95 Control Hierarchy

S95 Part 1 defines the interfaces between business logistics systems and manufacturing operations systems. Part 2 doesn't add any new concepts to the integration model, but it contains additional details and examples to help explain and illustrate the Part 1 objects. Part 3 defines models for the disparate collection of activities that must occur in manufacturing operations for effective and efficient manufacturing. The goal is to provide manufacturing companies with a common language to describe requirements to vendors and let companies compare alternate architectures and solutions.[3]

Upcoming S95 Parts 4 and 5 will address object models and attributes for Manufacturing Operations Management, as well as business to manufacturing transactions enabling information collection, retrieval, transfer, and storage in support of enterprise/control system integration.

"Shop Floor to Top Floor" Integration

S95-compliant MES systems fill the complicated gaps between the "top floor and the shop floor," linking business systems and the core automation, controls, and HMI/SCADA, and pure manual data collection systems existing in the manufacturing environment - *Figure 3*.

Although the S95 standard includes a model similar to S88 that defines terms and transactions, the scope of S95 goes on to define activities and models at all levels of the production process. Users who purchase systems from different suppliers for different levels of the organization can have confidence that they will understand how they communicate along with finding greater ease with the integration process if both are compliant with the S95 standard.[4]

tems, and other Enterprise Resource Planning (ERP) applications.

The MCS provides a platform for handling both inbound transactions (i.e., process orders and lab results) and outbound transactions (i.e., inventory updated and lab requests) - *Figure 4*.

Typical MES/PCS Transactions

The benefits of the unified MCS approach are demonstrated through MES/PCS transactions, such as production execution, resource management, material tracking, and electronic work instruction management. Unit procedural control and phase execution with an MCS is more efficient than in a traditional environment with separate system domains. Transactions between different systems and personnel are seamless; operators see a unified interface with a common HMI environment, instructions, and displays.

Production Definition, Dispatching, and Execution

With the unified MCS architecture, orders from MRP come down to the plant floor through the MES - *Figure 5*. The MES automatically dispatches recipes based on required equipment statuses and availability, and executes them in the process control system. This innovative approach eliminates the traditional requirement for operators to manually check equipment status, assign equipment, load recipes, and initiate batch execution. Rather, the MES handles these activities as the operator fulfills the order at the PCS layer.

Consider a typical MCS batch processing application: after dispatching a unit procedure, the MES binds to the process unit for execution and starts the sequences. The PCS then executes phases within operations at the equipment level, performs automated tasks, and requests information from the MES.

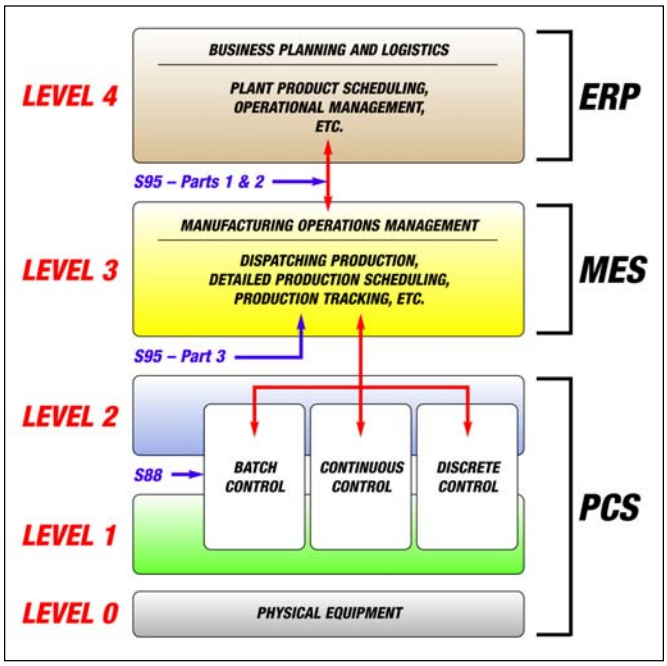


Figure 3. S95 control hierarchy levels.

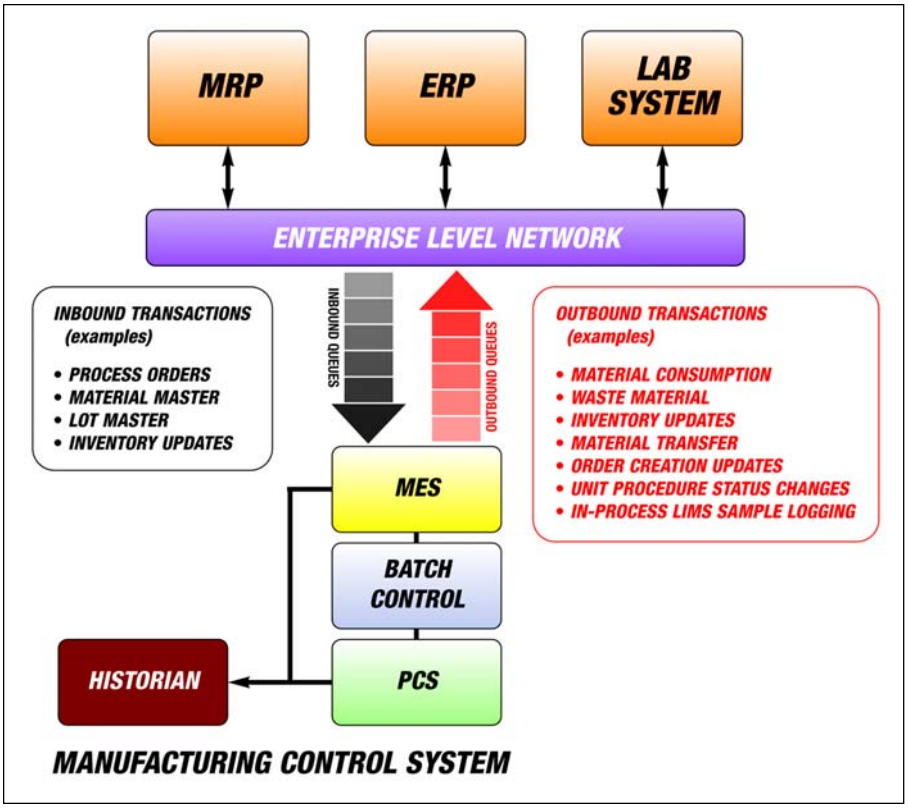


Figure 4. Typical system transactions.

Management of Resources and their Statuses

At a typical pharmaceutical or biotech plant, operators are tasked with managing production resources and reporting on their statuses. The operator must verify the status of specified equipment in a paper log or database before a batch can be started or progressed.

The MCS solution automates this procedure since the programmed phase in the PCS controls specific equipment. The phase is designed to automatically request equipment and assets from the MES based upon their required status. PCS requests for information are handled by a transaction executed to the MES via an OPC service. The MES automatically allocates resources and performs arbitration should conflicts arise. This allows the automation process to continue without interruption.

For example, The PCS might issue requests such as, "This tank is needed - is it sterile?" The MES will respond, "Yes, you can acquire this resource because its status is correct for your requirements." Once the operation is completed, the PCS phase will release the tank back to the MES with a message saying, "This equipment is being returned with a status of 'dirty.'" Such transactions are carried out automatically, without operator intervention.

Material Management and Tracking

When it comes to material tracking and reporting, the PCS phase again interfaces directly with the MES, which in turn, interfaces with Manufacturing Resource Planning (MRP) as required for inventory updates. During execution of a particular phase, the system might say, "Material 'A' for the batch is needed." The MES then reports, "The material's quality is acceptable and the expiration date has not been exceeded. Here is the quantity that should be added." It then provides results regarding bar code scanning and performs system data verification at the point of use (i.e., when the material is introduced into the batch).

When tracking material consumption, the PCS can send a transaction notifying the MES that it is time to automatically or manually consume a particular additive or ingredient. As the automated steps execute, a procedure pops up on the operator's screen with prompts for completing the task.

Under normal circumstances using disparate MES and PCS systems, the operator has to pull up a ticket or paper-on-glass in the MES environment to check the status of materials, and verify information indicating that he is adding the prescribed material. Then, he must acknowledge the material addition is complete and instruct the PCS to continue execution.

In the case of manually consumed materials, standard material add pages prompt the operator to scan the required material and then automatically execute the quality checks prior to prompting the operator to deliver the material. For automatically added materials, the quality checks and consumption reporting are done without operator intervention unless required.

Management of Electronic Work Instructions

The MCS strategy also revolutionizes the handling of electronic instructions and workflows and eliminates paper procedures. Unlike a standalone MES, the integrated system automatically presents instructions or workflows (i.e., SOPs) on the HMI screen whenever and wherever they are needed. Operators are no longer burdened with coordinating MES activities, while staying abreast of PCS execution. This enables a new level of plant production efficiency.

During a phase execution, for instance, the system calls up standard faceplates on the process control graphic that prompts the operator whenever his attention is required. The operator is presented with an "action list" displaying phases with their instruction, a button to display the detailed instruction, and upon acknowledgement of the action, the type of signature required. Operator instructions can be signed off directly from the HMI page - *Figure 6*.

Likewise, in the middle of a phase, required manual actions can appear on the MES page as a workflow that includes a variety of MES activities the operator must follow. Once the tasks are completed, the technician acknowledges the work with an electronic signature and the PCS resumes automated control.

Discussion

For pharmaceutical and biotech operations, the unified MCS not only delivers new automation capabilities, but also presents new ways to manage manufacturing complexity and improve operational efficiency. Industry analysts estimate that as much as 20% of a firm's costs of operations are associated with manufacturing, which means even modest operational improvements can have a significant financial impact.[6]

Greater People Collaboration

For a plant's technology personnel, the MCS merges disparate MES and automation departments into an integrated production team that works hand-in-hand to optimize manufacturing operations. Under the new architecture, components such as work instructions, bill of materials, and asset definitions are supported in the MES, but requested from phases executed in the PCS. As a result, the two departments interact to ensure components are correctly configured and managed. This closer collaboration enabled a reduction of support staff between the two departments of over one-third and the restructured groups operate as a single organization as opposed to separate teams of engineers and IT specialists.

In addition, manufacturing personnel, quality departments, and engineering staff now utilize a single, unified system with a common environment for accessing production data, viewing process displays, and making critical operational decisions.

Faster Review and Product Release Processes

The MCS solution eliminates the need to manage paper batch records. The system provides electronic records of each batch of products produced, as well as the means to collect, store,

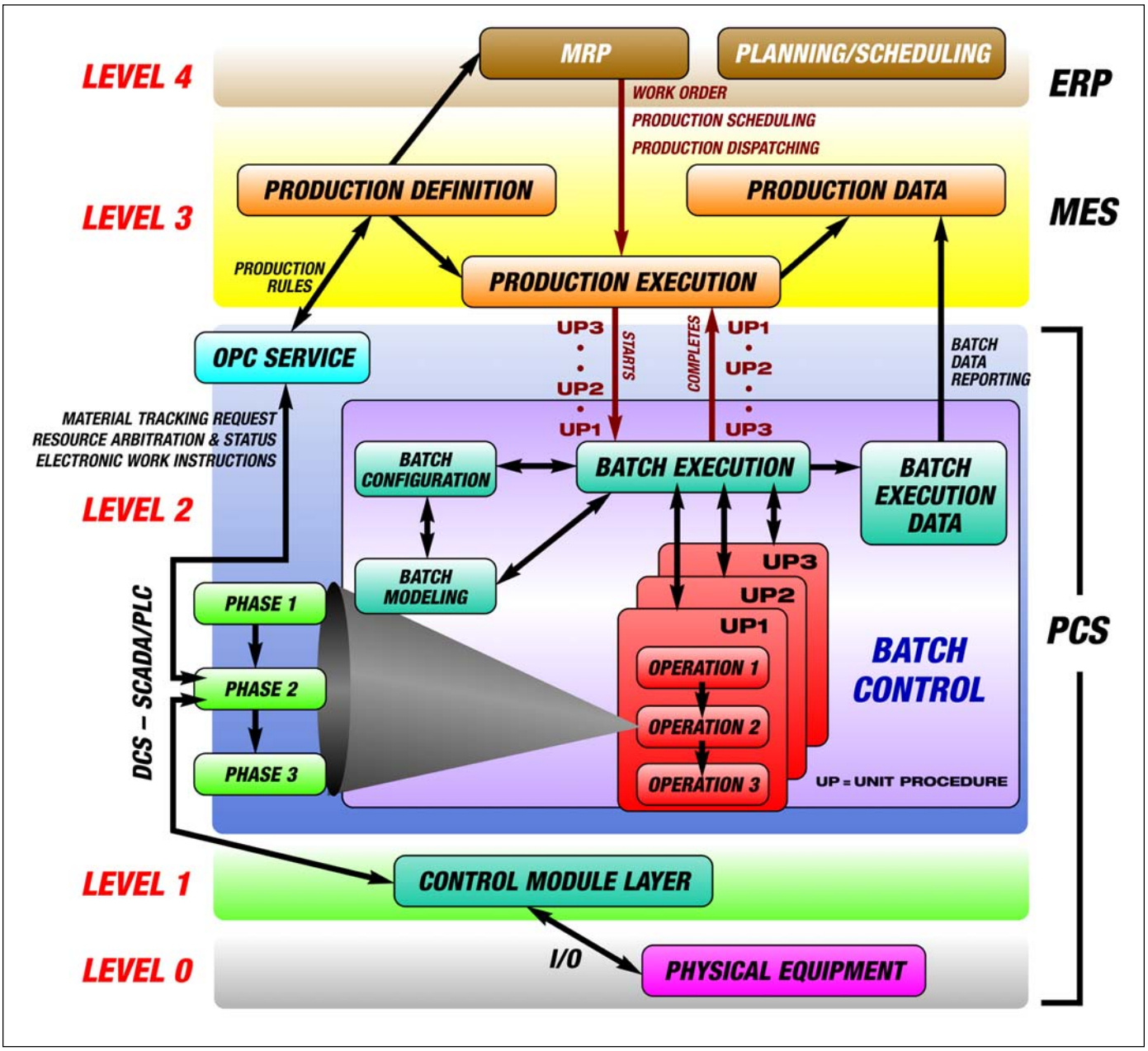


Figure 5. Unified MCS architecture.

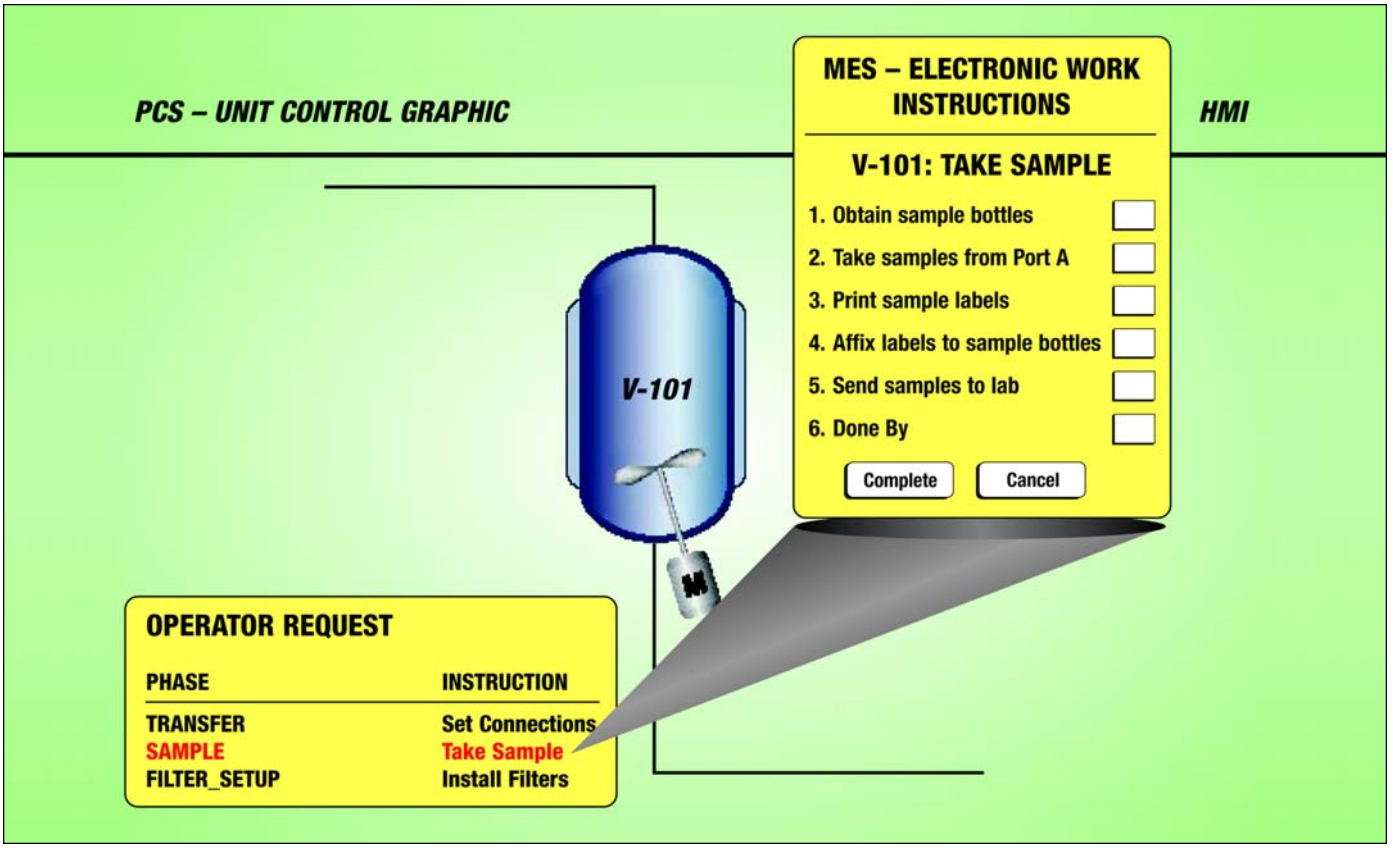


Figure 6. Unit control graphic.

and analyze data more efficiently. Documents within regulated environments can be created, reviewed, approved, and issued electronically in a collaborative manner with full change control by the respective departments. This approach simplifies the GMP-related document management process.

Manufacturers implementing MCS can streamline the effort required for regulatory compliance and expedite the release of manufactured product. The integrated system, with EBR and process automation information (i.e., alarms, unit control data, batch events, process history, etc.), enables easier compliance and verification. The plant's quality group can access robust, consolidated data assisting the review process prior to product release.

Previous paper-based systems required numerous weeks to collect paper records, review, reconcile discrepancies, and approve for release. Subsequent designs of disconnected MES and PCS architectures reduced the product release process to a couple of weeks, but the new MCS design is estimated to reduce this process to a few hours.

Better Information Equals Improved Performance

The integrated MCS system approach brings together information from key areas such as process control, MES, and laboratory systems. This facilitates the discovery of new opportunities to improve operational performance and drive down costs.

Pharmaceutical and biotech facilities gain a world-class solution providing a single source of centralized manufacturing data. No longer must PCS data be duplicated for the MES environment, and then migrated into the ERP system. Instead of distributing asset and process information between three different systems, users attain a "Single-Source of Truth."

Equally important, an interoperable MCS design with Web/HTML-based applications and open, industry standard communications protocols provides a secure and predictable path for future technology investments. Potential directions can include RFID, biometric security, and wireless hand-held mobile devices, to name a few.

Conclusion

In the life sciences industry, the constant challenges for manufacturing are efficient, streamlined operations with fewer errors, greater consistency, and unfailing compliance with FDA regulations. Manufacturers seek shorter product cycle times, faster product changeover, and better maintenance scheduling - all adding up to improved operational performance.

To meet these challenges, a seamless MCS architecture providing common electronic batch records and production reporting for automation and production management with reliable traceability (i.e., materials, equipment, and personnel) can be employed as presented in this article.

Traditionally, many manufacturing facilities have had a disconnected view of their automation and IT solutions. As the lines between systems blur, a paradigm shift is likely to move the industry toward the next-generation MCS, merging current MES and PCS with integrated batch control technology. As this natural evolution progresses, companies will

actualize the benefits of managing plant-level and corporate-level systems as part of a single system. And, unified enterprise architectures, as discussed in this article, will likely emerge as the standard manufacturing solutions for new facilities by the end of this decade.

Acronyms

EBR	Electronic Batch Records
ERP	Enterprise Resource Planning
IT	Information Technology
HMI	Human Machine Interface
MES	Manufacturing Execution System
MRP	Material Resource Planning
PCS	Process Control System
PC	Personal Computer
OLE	Object Linking and Embedding
OPC	OLE for Process Controls
RFID	Radio Frequency Identification
SCADA	Software Control and Data Acquisition
UP	Unit Procedure
XML	Extensible Markup Language

References

1. Menendez, R. E., "A New Suite of Automated Bioreactors at Genentech: A Case-Study Employing Standards, Guidelines, and Software: From Requirements to Validation," *Pharmaceutical Engineering,* Nov/Dec 2004, Vol. 24, No. 6, pp. 8-16.
2. Parshall, J. and Lamb, L., *Applying S88 Batch Control from a User's Perspective*, ISA, 2000.
3. *Enterprise Integration Takes the Fast Track*, InTech, September 2001.
4. Mintchell, G., "Drive Integration with Standards," *Automation World,* September 2004.
5. U.S Food and Drug Administration, *Guidance for Industry Part 11, Electronic Records; Electronic Signatures – Scope and Application*, August 2003.
6. *Implementing Manufacturing Execution Systems in the Pharmaceutical and Biotech Industry*, Center for Business Intelligence, August 2006.

About the Authors

Ronald E. Menéndez has more than 16 years of automation experience within the biopharmaceutical, pharmaceutical, chemicals, and consumer goods industries, and is experienced in a variety of control system platforms and batch management software. He is a Senior Automation Engineer in the Corporate Engineering Department at Genentech's headquarters in South San Francisco, California, where he currently serves as the lead design engineer of the control system and MES for Upstream operations at a new bulk manufacturing facility in Vacaville, CA. Previously, he worked for the Sequencia Corporation, where he contributed to the development of batch management software in the early 1990s; performed system integration and plant start-ups in Latin America, Southeast Asia, and Europe; and provided S88 consulting to control system vendors, biopharmaceutical and pharmaceutical manufacturing companies. He holds a BS in chemical engineering from the University of California, Santa Barbara. He can be contacted by e-mail at menendez.ron@gene.com.

Genentech, 1000 New Horizons Way, MS# 181/Rm. # 81002, Vacaville, California 95688.

Darrell Tanner has 17 years of experience in the process automation industry designing, developing, and delivering solutions to the life sciences, consumer goods, and chemical industries. He is currently the Honeywell Technical Lead for Genentech's new bulk manufacturing facility in Vacaville, California. He has a BS in chemical engineering from Arizona State University. He can be contacted by e-mail at darrell.tanner@honeywell.com.

Honeywell, 3079 Premiere Pkwy., Duluth, Georgia 30097.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Pharmaceutical Standards for Computerized Systems

This article compares the requirements in the 21 CFR Part 11, EU GMP Annex 11, and Part 11's EU counterpart PI 011-2.

by Siri H. Segalstad

Introduction

GxP is the term used to refer to pharmaceutical and associated life science regulations, including those covering manufacturing (Good Manufacturing Practice - GMP), non-clinical testing (Good Laboratory Practice - GLP), and clinical testing (Good Clinical Practice - GCP).

IT systems may have a direct or indirect impact on the product quality in various ways. Such IT systems are generally called GxP systems. These systems include, but are not limited to, systems handling materials used in the production, production planning and control systems, laboratory systems, and systems for non-clinical and clinical testing. Document management systems also may be regarded as GxP systems if they handle the quality system and Standard Operating Systems (SOPs), or if they handle production documents and validation documents.

The GxPs themselves do not say very much about IT systems so appendices and/or added standards have been created to make people understand how the authorities expect IT systems to be handled. In an old version of the EU GCP, the only requirement for computer systems was "Computer systems shall be validated and error free." The next version had removed the requirement "error free…"

For medical devices,[1,2] IT systems are used in two different ways: one is when the IT system is used during development, production, and control of the medical device, just like it is for any other pharmaceutical product. In this case, the system should be handled the same way as GxP IT systems. The other case is when the system is, or is part of, the medical device itself. Some of these medical devices are implanted in the body. A pacemaker is an example of that. Others are used for *in vitro* (outside of the body) testing, e.g., testing for allergies, where the test instrument may be regarded as a medical device.

A pharmaceutical company selling to the EU market must comply with the EU regulations, and a company selling to the US market must comply with the US regulations, regardless of where the company is developing or manufacturing its goods.

The GxP Requirements for IT Systems

European GxP Requirements for IT Systems

GMP: The EU GMP added Annex 11[3] to explain what the regulators considered was needed for computerized systems. Annex 11 originated as PIC/S[4] GMP Annex 5 in 1991 and was later adopted by the EU GMP as Annex 11 and also is now Annex 11 in the PIC/S GMP.[5]

Annex 11 has 19 clauses covering what the inspectors expect, but it is not very useful as a tool to tell how to get there. Adding the fact that the standard is now very old, it is about time to revise it. As of February 2007, it is still the current requirements for IT systems.

Pharmaceutical Inspection Cooperation Scheme (PIC/S)[4] which is the organization for cooperation between regulators and inspectors, also thought it was about time to revise it, especially after the FDA had created the 21 CFR Part 11 with its relatively detailed requirements.

The PIC/S finalized their interpretation document 20 August 2003 under the name PI 011-1 Good Practices for Computerized Systems in Regulated "GxP" environments. The current version is PI 011-2[6] from 1 July 2004. When inspectors get together and create a document like this, it is worth paying careful attention to it.

GLP has long used the OECD Monograph 116[7] for the pharmaceutical industry, which is

better detailed than the old GMP Annex 11. The new PIC/S document also covers GLP.

GCP adopted the GMP Annex 11, and the new PIC/S document also covers GCP.

The three major documents for IT system compliance in the pharmaceutical EU and US all have a number 11 in their document number. This is probably a coincidence; at least the author is not aware of any reason why they all include this number.

21 CFR Part 11

21 CFR Part 11 Electronic Records; Electronic Signatures[8] was created after the industry requested guidelines for compliant use of electronic signatures in the early 1990s. The first draft was made public and received a lot of comments, some of which were contradictory. The FDA issued the final version on 20 March 1997 and had expectations that industry would be able to be in compliance four months later, by 20 August 1997. The industry was surprised to see that very little of the

Topic	US 21 CFR Part 11	EU GMP Annex 11	PIC/S PI 011-2
Validity of Standard	11.1 This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in Agency regulations....	Not mentioned, but it is an annex to GMP.	3.2 It is not intended to be a barrier to technical innovation or the pursuit of excellence. The advice in this Guidance is not mandatory for industry. However, industry should consider these recommendations as appropriate.
Closed / Open Systems	11.10 and 11.30 defined	N/A	19.7 The words are not used, but the difference is made, and handling is about the same as in Part 11.
Validation	11.10(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.	2 The extent of validation necessary will depend on a number of factors, including the use to which the system is to be put, whether the validation is to be prospective or retrospective, and whether or not novel elements are incorporated. Validation should be considered as part of the complete life cycle of a computer system.	Included in all, but five of its 24 clauses or chapters. These include several requirements, many with reference to GAMP 4 for how to do it.
Copies of Records	11.10(c) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the Agency.	12 For quality auditing purposes, it should be possible to obtain clear printed copies of electronically stored data.	21.10 The ability exists to generate accurate and complete copies of records in both human readable and electronic form.
System Access	11.10 (d) Limiting system access to authorized individuals.	8 Data should only be entered or amended by persons authorized to do so.	21.10 Access to records is limited to authorized individuals.
ID and Password Issuance	11.300(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).(c) Following loss management procedures to electronically reauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls. (d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and as appropriate, to organizational management.	8 ....Suitable methods of deterring unauthorized entry of data include the use of keys, pass cards, personal codes, and restricted access to computer terminals. There should be a defined procedure for the issue, cancellation, and alteration of authorization to enter and amend data, including the changing of personal passwords. Consideration should be given to systems allowing for recording of attempts to access by unauthorized persons.	19.2 • The management and assignment of privileges • Levels of access for users 19.3 ...basic requirements are satisfied: • Access rights for all operators are clearly defined and controlled, including physical and logical access. • Basic rules exist and are documented to ensure security related to personal passwords or pass cards and related system/data security requirements are not reduced or negated. • Procedures are in place to ensure that identification code and password issuance are periodically checked, recalled, or revised. Loss management procedures exist to electronically invalidate lost, stolen, or potentially compromised passwords. The system should be capable of enforcing regular changes of passwords. • Procedures identify prohibited passwords. • An audit log of breaches of password security should be kept and measures should be in place to address breaches of password security. • The system should enforce revoking of access after a specified number of unsuccessful logon attempts.

Table A. Overview of Requirements in Part 11, Annex 11, and PI 011. The table includes the reference to paragraph or chapter in standard. The text is only an excerpt. For the full text and context please read the standard. *(Table is continued on page 98.)*

regulation actually covered the electronic signatures, while the majority of the text covered electronic records. However, it does make sense: you can only trust the electronic signature if the electronic records can be trusted.

21 CFR Part 11 is nicknamed "Part 11." People who have worked with IT systems in the pharmaceutical industry in the roles of key personnel, validation experts, or quality assurance, are already familiar with Part 11. Numerous publications have been written about the requirements and how to comply with them. The exact interpretations of the requirements vary. The FDA also added to the confusion by first issuing a number of draft guidance documents making the interpretation of the regulation stricter, more and more prescriptive, and then suddenly withdrawing them all while issuing one new draft guidance document where risk-based approach is a key factor.[9] In this, it is up to the discretion of each organization to assess the importance of their computer systems and handle the high-risk and lower-risk systems appropriately. The risk assessment itself must be documented. It focuses on risk assessment, but does not go into detail on how to handle the risks – risk management.

Part 11 has two main sections: one on electronic records, and one on electronic signatures. There is no requirement for using either, but if IT systems are used, they need to be in compliance with the electronic records requirements. It is optional to use electronic signatures, but if E-signatures are used, the E-signatures also must comply with the requirements.

The GxPs are called "predicate rules" to the 21 CFR Part 11. These cover a lot of details not mentioned in 21 CFR Part 11. The document is not to be read instead of the GxPs, but in addition to them. One example is the section on electronic signatures that does not say anything about where or when signatures are needed. The user must find this in the applicable GxP. Then, if the computer system in question shall be used for E-signatures, those Part 11 requirements apply. Another example is that Part 11 does not state that there shall be given a reason for data changes in the system. This is required by the predicate rules.

EU GMP Annex 11

EU GMP Annex 11, or just "Annex 11," is basically a list of things that must be in place for computerized systems used in the pharmaceutical industry. It is not a prescriptive description of what to do and it includes little detailed guidance. It can be used as a checklist for an organization to see if they comply, but only if the organization understands the intent behind the words in the document.

PIC/S Guidance - PI 011-2

This document provides an EU perspective on electronic records and signatures, as well as the wider aspect of the use of computerized systems in the GxP environment, including advice on what to take into consideration when implementing and validating a system.

PI 011 has references to ISO,[10] IEEE,[11] ISPE,[12] and GAMP,[13] in addition to Part 11[8] and Annex 11.[3] It encourages the use of the existing standards, instead of repeating the same advice. But also it warns that no standard should ever be followed without understanding how one's own organization works. It is refreshing to see that we are encouraged to think.

It is surprising that the references to the ISO standards[10] include 1995 versions and not the 2000 versions, which were available four years before the PI 011-2 document was finalized.

It is quite obvious that Part 11 has been scrutinized when creating this document. A lot has been done to make it a better and more useful document than Part 11. It covers much of the same areas as Part 11, but some details are spelled out in a much clearer way.

GAMP

Good Automated Manufacturing Practice (GAMP)[13] was started as an industry initiative to explain to the pharmaceutical industry exactly what computer systems validation was, in order to fulfill the regulatory requirements. These requirements were very hard to translate to "what do we actually do to validate our computer system."

The first version came in 1995, and now, more than 10 years later it is a widely-used industry guidance document, and is referred to by the FDA and the European agencies. The current version is GAMP 4.[14] The GAMP organization is a Community of Practice within ISPE,[12] where many people around the world take part in preparing various good practices guidance documents.

ISPE has issued several guidance documents as answers to the new regulatory initiatives, e.g., for Part 11 Risk-Based Approach to Validation,[15] Laboratory Systems,[16] Testing of GxP Critical Systems,[17] IT Infrastructure,[18] Calibration Management,[19] and Global Information Systems.[20] They also have published Position Papers on topics, including Building Management Systems.[21] Each of the guides has detailed suggestions for how to practically deal with the topics in question.

ISO 9000-Series

The ISO 9000-series standards are not pharmaceutical regulations, but are still useful for pharmaceutical companies.

The ISO 9000 currently exists in a six year old version as ISO 9000:2000.[22] This standard describes requirements for a quality management system in a quality managed organization.

ISO 9001:2000[23] describes how to develop, manufacture, and test products, and how to deal with customers and suppliers. ISO 9001 is a certifiable standard. This means that a company, who chooses to comply with the standard, can get an accredited standards organization to assess their compliance, and issue a certificate to prove that they are following this.

ISO 9001 is easy to use for a company producing tangible items. Software is an intangible product, and ISO 9001 is not equally good for software. A guideline to ISO 9001 was created to tell how to deal with software. This was called ISO 9000-3, and has existed in several issues. In its newest edition it is called ISO 90003:2004.[24] The standard explains

how a software vendor shall plan, program, test, and support software. When a software company wants to be ISO 9001 certified, it is normally done "under the TickIT Scheme," i.e., the TickIT[25] Guide and ISO 90003 are followed.

A pharmaceutical company will quite often perform a vendor audit on its major software suppliers, and the ISO 90003 standard tells what to expect from the vendor. Publications also have been written on this issue.[26, 27] The TickIT Guide is very useful as additional reading of what to expect. In principle there is no difference between what is normally done in a pharmaceutical company and what a software vendor shall do: plan what to do, do what you plan, and document what you have done.

GAMP 4 also covers vendor audits in an appendix, but in this author's opinion that appendix is a bit thin. ISO 90003 gives a more thorough basis for understanding what needs to

Topic	US 21 CFR Part 11	EU GMP Annex 11	PIC/S PI 011-2
Electronic Signature Uniqueness	11.100 (a) Each electronic signature shall be unique to one individual and shall not be reused by or reassigned to anyone else. 11.300 (a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.	N/A	20.4 It is expected that appropriate controls will exist such as the maintenance of a register of authorized users, identification codes, scope of authorized actions, in support of GxP electronic records. 21.5 An appropriate form of Electronic signature or authentication/identification • Should be applied where external access can be made to a computerized GxP system • The system electronically generates GxP regulatory records or key decisions and actions are able to be undertaken through an electronic interface and electronic signatures.
Electronic Signature Components	11.200 (1) Employ at least two distinct identification components such as an identification code and password.	N/A	21.8 • A unique combination of user ID and password called for by the computerized system and linked to the user's authorized account for the use of a specific application. • Permitted task functionality for that user
Audit Trail	11.10.(e) (e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records.	10 Consideration should be given to building into the system the creation of a complete record of all entries and amendments (an "audit trail").	21.10 Secure, computer-generated, time-stamped audit trails to independently record GxP related actions following access to the system are used.
Data Changes	11.10(e) Record changes shall not obscure previously recorded information.	10 Any alteration to an entry of critical data should be authorized and recorded with the reason for the change.	20.1 All original data records and masters and any subsequent alterations, additions, deletions, or modifications are to be retained accurately and comprehensively within the retrievable audit trail.
Training	11.10(e) (i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.	1 Persons in responsible positions should have the appropriate training for the management and use of systems within their field of responsibility which utilizes computers. This should include ensuring that appropriate expertise is available and used to provide advice on aspects of design, validation, installation, and operation of computerized system.	15.3 Records of operator training (introduction and on-going training). 20.1 Firms will need clearly documented policies, standard operating procedures, validation reports, and training records covering such system controls. 21.0, 22.6 Other training covered
Genuine E-signature	11.200(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.	N/A	Definitions: (a) It is uniquely linked to the signatory. (b) It is capable of identifying the signatory. (c) It is created using means that the signatory can maintain under his control. (d) It is linked to the data to which it relates in such a manner that any change of the data is detectable.
Risk Assessment	Included in the draft guidance document	N/A	15.2 For all critical systems, a holistic risk-based approach is necessary. This should consider the risks from the entire pharmaceutical application.
Risk Management	N/A	N/A	Reference to DISC PD 3002 Guide to BS 7799 Risk Assessment and Risk Management (ISBN 0 580 29551 6).

Table A. Overview of Requirements in Part 11, Annex 11, and PI 011. *(Continued from page 96.)*

be included in the checklist. PDA Technical report 32[28] also is useful when planning a vendor audit.

Comparison Between the Standards

There are no contradictions in the requirements in the three standards 21 CFR Part 11, EU GMP Annex 11, and PI 011-2, but there is a large difference in how much they actually tell the reader.

Annex 11 is short and concise, but very difficult to use unless one actually understands what to do.

Part 11 has been interpreted differently over the years. Some of this has a root cause in warning letters from inspections; some in what an inspector has publicly said, which immediately has been understood as *the* interpretation of the requirement; some have been various interpretations where the pendulum has moved from one extreme to the other.

The FDA Guidance for Industry on the Scope and Application of Part 11[13] has clarified the FDA position and their interpretation of Part 11.

The FDA is currently re-examining Part 11 and is expected to issue a revised regulation for comment.

PI 011-2 is a lot bigger and includes discussions of several of the items. Many of these discussions have references to further reading in other standards, and GAMP 4 is one of them. The application of risk-based approach is heavily emphasized. There also is a distinction in typeface to tell whether the text is explanatory (normal) or what the inspector expects to see (italic). Even people in US companies will do well making themselves familiar with this document, as it gives a lot more detail to what Part 11 only states as expectations.

Differences

The differences between the standards and regulations are generally in the words and level of details in and not in the requirements or interpretation.

Standards generally cater to one specific type of organization: The ISO 9000-series is meant for manufacturers, regardless of whether they make safety pins or cars; the GxP regulations are meant for the pharmaceutical development, testing, and production; Part 11 and Annex 11 has the end-user as their primary focus, but Annex 11, while addressing the integrity of electronic records does not cover electronic signatures. PI 011-2 also has a section on some of the vendor's responsibilities for creating the software in a quality environment, and suggests use of a few standards for that purpose as well as inspector's expectations. GAMP has chapters for the system developers, i.e., the vendors for how to develop the system in a quality environment; chapters for the QA auditor so that they will know what to look for when conducting a vendor audit; and chapters for the end users so they know how to validate their system.

GAMP 4 is the most detailed document. This also is the only one that explains in detail how to fulfill requirements, instead of just stating the requirements.

Probably the most significant difference is the level of detail in validation descriptions. While Part 11 mentions the word "validation" once in §11.10(a), detailed requirements and expectations of the validation effort are described throughout the PI 011 document. Annex 11 includes a short description, and GAMP 4's 200+ pages are dedicated to all practical aspects of validation.

Risk assessment is included in the FDA Guidance for Industry on the Scope and Application of Part 11, and also is in PI 011-2. GAMP 4 includes a separate guide for risk-based approach to validation of computerized systems.

Similarities

When looking at the three documents Part 11, Annex 11, and PI 011-2, we can see that there are few requirement differences. The words may be different, and the level of detail is certainly different, but the content is basically the same. None of the documents have requirements that can not be read into each of the other documents, perhaps with exception of electronic signatures, which is not mentioned in Annex 11.

The risk-based approach has been adopted both by the US FDA and the European authorities, and is now the current way of thinking.

Table A gives a selected overview of the various standards' coverage of some of the requirements.

Conclusion

Companies have done a lot of work during the past seven to eight years to make sure that their systems are Part 11 compliant. Systems that are Part 11 compliant also are likely to be compliant with many aspects of the EU requirements set forth in Annex 11 and interpreted in PI 011-2.

PI 011-2 has a lot of suggestions and details that FDA regulated companies can benefit from, and they should be encouraged to examine it, even if the organization does not have to comply with EU regulations.

GAMP 4 and its associated Good Practice Guides all cover various aspects of validation. These various guides reflect EU and US regulatory requirements and expectations, and give good practical advice on what needs to be done. The GAMP guides are useful tools; however, none of the guides should ever be used directly with copy-and-paste. All organizations work differently and you must make sure you still assess your organization and your way of working. In other words: thinking is still encouraged.

If you are still unsure of how to handle the computerized systems, the author can recommend one of the good classes that ISPE/GAMP are giving around the globe during any one year.

References

1. US Medical Device Regulations: US 21 CFR 820 Quality Systems Regulation, Medical Devices. US 21 CFR 821 Medical Device Tracking Requirements.
2. EU Medical Device Regulations: Council Directive 93/42/EEC of 14 June 1993 concerning Medical Devices.
3. EU GMP Annex 11: EU Annex 11 to the EU Guidelines of Good Manufacturing Practice for Medicinal Products.

4. PIC and PIC/S: Pharmaceutical Inspectors Convention PIC/Pharmaceutical Inspection Cooperation Scheme PIC/S http://www.picscheme.org.
5. PIC/S GMP: Document PE 009-5, 01 August 2006 http://www.picscheme.org.
6. PI 011-2 Good Practices for Computerised Systems in Regulated "GXP" Environments 01 June 2004 http://www.picscheme.org.
7. Monograph 116: GLP Consensus Document 'The Application of the Principles of GLP to Computerised Systems,' 1995, OECD/ OCDE/GD (95) 115 (Environment Monograph No.116).
8. 21 CFR Part 11: US FDA Register 21 CFR Part 11 Electronic Records and Electronic Signatures www.fda.gov.
9. Guidance for Industry, Part 11, Electronic Records; Electronic Signatures – Scope and Application, US Dept. of Health and Human Services and all FDA Centers/Offices, September 2003. www.fda.gov.
10. ISO Standards: www.iso.org. ISO standards can be purchased from the national standards organizations, often in the native language in addition to English.
11. IEEE organization: www.ieee.org.
12. ISPE: www.ispe.org.
13. GAMP: www.ispe.org/gamp.
14. *GAMP® 4, Good Automated Manufacturing Practice (GAMP®) Guide for Validation of Automated Systems*, International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001, www.ispe.org.
15. *GAMP® Good Practice Guide: A Risk-Based Approach to Compliant Electronic Records and Signatures,* International Society for Pharmaceutical Engineering (ISPE), First Edition, April 2005, www.ispe.org.
16. *GAMP® Good Practice Guide: Validation of Laboratory Computerized Systems,* International Society for Pharmaceutical Engineering (ISPE), First Edition, April 2005, www.ispe.org.
17. *GAMP® Good Practice Guide: Testing of GxP Systems,* International Society for Pharmaceutical Engineering (ISPE), First Edition, December 2005, www.ispe.org.
18. *GAMP® Good Practice Guide: IT Infrastructure Control and Compliance,* International Society for Pharmaceutical Engineering (ISPE), First Edition, August 2005, www.ispe.org.
19. *GAMP® Good Practice Guide: Calibration Management,* International Society for Pharmaceutical Engineering (ISPE), First Edition, December 2001, www.ispe.org.
20. *GAMP® Good Practice Guide: Global Information Systems Control and Compliance,* International Society for Pharmaceutical Engineering (ISPE), First Edition, October 2005, www.ispe.org.
21. ISPE GAMP Forum – BMS SIG, "Position Paper: Use of Building Management Systems and Environmental Monitoring Systems in Regulated Environments," *Pharmaceutical Engineering,* September/October 2005, Vol. 25, No. 5, pp. 28-78).
22. ISO 9000:2000 Quality Management Systems – Fundamentals and Vocabulary.
23. ISO 9001:2000 Quality Management Systems – Requirements.
24. ISO 90003:2004 Guidelines for the Application of ISO9001:2000 to Computer Software.
25. The TickIT Guide Using ISO 9001:2000 for Software Quality Management System Construction, Certification, and Continual Improvement, Issue 5.0, ISBN 0-580-36743-9, DISC TickIT Office, January 2001, www.tickit.org.
26. Segalstad, Siri, "Vendor Audits for Computer Systems: An ISO 9000-3 Approach," *Laboratory Automation and Information Management,* 32, (1996), pp. 23-31.
27. Segalstad, Siri, "Supplier Auditing and Software," *European Pharmaceutical Review,* Vol. 1 Issue 3, (1996), pp. 37-44.
28. PDA Technical Report No. 32, "Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations," PDA 1999, www.pda.org.

Acknowledgement

I would like to express my gratitude to Siôn Wyn who made corrections and improvements to this article.

About the Author

Siri H. Segalstad has worked with quality assurance/validation of IT systems since late 1980s, and started her own consulting company in 1995. During the past 11 years, she has worked with a variety of pharmaceutical companies with a variety of validation tasks. She is also involved in an EU project where the goal is to create a complete curriculum for a Master's degree in IT validation. Segalstad is in charge of four classes for basic and advanced Quality Management Systems, Validation, and LIMS. She has written a number of publications on LIMS and validation issues, and has given presentations and classes in more than 20 countries from Taiwan in the East to California in the West. She can be contacted by e-mail at: siri@segalstad.com.

Segalstad Consulting AS, PO Box 15 Kjelsas, N-0411 Oslo, Norway.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

The FDA Answers Your Questions on Barrier Isolation Technology

The following questions and answers were provided by panelists Rick Friedman and Bob Sausville during the ISPE 15th Annual Barrier Isolation Conference, held in June 2006. These responses do not necessarily represent the positions or policies of the FDA. They are simply the panelists' interpretations of these cGMP matters and are based on their collective experiences with isolator technology.

RABS

1Q Many companies are evaluating the RABS vs. barrier isolator decision for use in their new facilities. Recognizing that there are product-specific or economic reasons to choose one technology over the other, and when all other factors are equal, the issue of regulatory acceptance becomes a major factor in the decision. Given the state of both technologies and the operational characteristics of each, does the FDA have an opinion regarding which technology should be chosen? Is there a preference for barrier isolators? Will that preference ever be codified?

1A The FDA would not tell a manufacturer that they must use a specific single technology to assure adherence to aseptic processing requirements. The FDA does indicate its general preference for isolators and provides corresponding regulatory incentives for them. A sound RABS concept also can provide added protection versus traditional processing approaches.

2Q Recent opinion suggests that a RABS line should use a VHP decontamination system if it is to be classed as an "Advanced Aseptic" Installation. In the 2005, ISPE RABS definition, this was not mentioned. What is the FDA position on an enterprise using a RABS installation in a Class 100 cleanroom (ISO5) without a VHP system? Will this be an acceptable installation and for how long - five years? 10 years?

2A While the FDA cannot forecast the future, a well designed and controlled RABS (automated VHP or a robust manual application of sporicidal agent) should exceed regulatory expectations at this time. Policy modifications generally take a long time to evolve. Also, the FDA's typical approach is to be essentially technology neutral, as we're a performance-based agency. You must adopt a design that achieves reproducible and compliant sterility performance in accord with GMP – how you get there is your decision.

3Q What specific types of validation relief can users of advanced aseptic processing expect?

3A First an isolator filling line is permitted to be in Class 100,000 surroundings, rather than the Class 10,000 used for most traditional lines. So that is a lower air cleanliness classification qualification hurdle.

During a media fill, advanced aseptic processing lines do not require the same run size as compared to more conventional or manually intensive processes. In the latter case, filling requirements need to be close or equal to normal batch size.

For isolators, significantly lower numbers of vials in a piggyback or staggered approach can generally provide an adequate assessment of media filling time to provide ongoing simulations of the campaign. While isolator line simulations generally simulate a lower proportion of the batch size versus traditional lines, initial simulations should have more vials to establish that baseline.

Media fill of all aseptic processing lines should be done semi-annually. When doing so for isolators, more flexible approaches to process simulation program and study design can be considered with respect to shifts. For example, instead of running a media fill with each separate shift on its own, one could, when appropriate, propose a study approach that includes overlapping of shifts. The rationale would be that the environmental affects of challenging shifts doesn't have much significance with use of an isolator. The people on the shifts still matter, of course. But the environmental effects of a shift change are normally not as meaningful anymore (unless there are other operational activities attendant to the shift change that might potentially impact the exposed sterile product in the isolator). In contrast, while RABS applications can represent a positive step forward, the shift-related issues of such non-isolated operations are still of significance.

4Q What are the issues, if any, the FDA sees with "open" interventions in RABS processing?

4A RABS units are, by definition, not generally meant to be open during production, a situation that adds undesirable variables that undermine the advanced processing model (such as impact on gloves surface by personnel, airflow dynamics).

5Q Is there a need for a material-of-construction study with disinfectants used for RABS inside?

5A Yes, any decontamination or disinfection qualification studies should be adequate to address different types of surfaces in the RABS. Any special surfaces or materials of variable finish need to be addressed. There is literature out there already to help you choose on which materials you want to focus your attention.

6Q Would you approve a RABS in Class ISO 8 if: 1. the doors cannot be open during operation (recorded during production)? 2. The validation has shown good decontamination and cleaning process? 3. All manual operations are made through gloves?

6A No, the FDA is willing to go to ISO 8 for isolators and well-designed Blow-Fill-Seal operations, but we do not believe this background environment would likely be appropriate for RABS. Firms are always welcome to bring such details of their design concept to the FDA's Field Office or Office of Compliance in their relevant Center (for purposes of discussion and feedback).

Isolators

7Q Since the FDA is not tasked with operator safety, regulation of toxic processing issues is not in their scope. However, due to the significant impact that safe handling requirements have on engineering controls, there is the potential for crossover impact with aseptic processing isolators. (The most obvious issue is positive vs. negative pressure). Additionally, there is a lot of discussion on safe handling for sterile liquids vs. powders, where some companies allowing RABS or even open fill operations for very hazardous products that require containment in powder form. Does the FDA have a position on containment of toxic products?

7A GMPs do deal with cross contamination issues. Although the Aseptic Processing guidance is intended to address positive pressure isolators, many of the concepts also apply to negative pressure isolators. Generally speaking, one should be careful in deciding whether it is appropriate to process a potent compound (especially those that are allergenic or particularly difficult to clean) on the same line as non-potent compounds. The FDA is working on detailed guidance on betalactam products and also is considering guidance beyond such products. The industry and the FDA are both very interested in developing guides on potent compounds – it would make sense to do so. One of the concepts is that degree of facility separation depends on your own scientifically rigorous risk assessment.

8Q How should instantaneous negative pressure excursions in an isolator be evaluated? (Example: negative pressure caused by half-suit manipulation).

8A This situation is not common and should result in a major investigation.

Environmental Monitoring

9Q To what extent can risk analysis and practical evaluation of risk in process reduce the need for microbiological monitoring of Isolators?

9A To a significant extent, environmental monitoring will always be needed, but less than on traditional lines.

10Q For a compounding isolator (cytotoxic products – negatively pressured), what methods of monitoring are used during the process? Same question for aseptic filling isolator and transfer isolators where classifications are Class 100 laminar flow and Class 100 turbulent respectively? Continuous air sampling methods? Are settling plates adequate and sufficient? Are fill needles monitored? Must gloves be sampled by RODACs or swabs?

10A Basic things that should be monitored do not change – yes for particles, continuous air sampling, remote active air monitoring often in at least two to three positions in a larger isolator. The FDA does not see settle plates that much in isolators. RODAC plates should be taken at the end of the campaign (e.g., 1X/week) and we want to see the gloves monitored. Monitoring the filling needles would depend on risk and level of manual activity in the area; we do not generally see this practice in isolators, but do see it rather frequently in traditional filling operations. Stopper hoppers, however, are often monitored.

11Q Preference between active air sampling vs. settling plates (passive).

11A Active air sampling is the FDA preference.

Glove Integrity

12Q For glove leak integrity testing, it seems we now have data to support the fact that a well-executed visual inspection with trained personnel is at least as efficient as an automated physical integrity test. If you accept that premise, do we still need to do the automated testing for micro holes? If yes, what is the rationale?

12A We do not necessarily accept the premise, and we will look for evidence that a visual inspection is well executed, using detailed procedures (with provisions for supervision, as appropriate). We will expect data from a physical integrity test. Guidance is clear that the combination of visual and mechanical is needed to provide the right level of assurance, in tandem with microbial monitoring of gloves.

13Q If there is a leak detected in a glove, must all product be rejected in the filling or simply the vials which are exposed (i.e., not stoppered)? Can the bulk be filled after the decon methods completed and re-ster-

ilization of equipment done? Must the bulk be re-filtered before filling?

13A Release is a layered issue, and to answer, one must get granular on what happened during the event. A firm may or may not reject, and then we would be glad to review a case with the individual questioner.

14Q In past ISPE Barrier Conferences, the practice of aseptic changing of isolator gloves was considered by some to be acceptable if the process was included during the execution of media fill validations and revalidations. Have any recent inspections or audits produced observations or concerns contrary to this acceptance?

14A We do not see aseptic changing of isolator gloves used – it was tentatively proposed during a Pre-Approval Inspection (PAI) by one user, and then voluntarily withdrawn. The particular firm had major problems demonstrating the practice during PAI. If you had a major problem with a glove, would you want to continue on? Quality by design can severely mitigate the impact of such an event.

15Q Can you share how a damaged glove that cannot be aseptically changed be taken out of service? Suggestions?

15A If you don't stop the fill, taking a very remote glove out of service has been attempted by some (no details offered on how). It would be critical for a firm to present a very convincing risk assessment to justify such a practice, based on scientific rationale.

16Q What is the Agency's position on glove leaks in non-filling areas – accumulators, post stoppering etc. (assuming a minor/pinhole leak)?

16A This situation may represent a lower risk if it occurs a significant distance from the sterile exposed product and its components, especially if the glove is not used. You need to fully explain the issue, explain why the glove did not affect product or potentially render the product non-sterile. It is possible that the glove was involved in a peripheral way during the fill, and if the campaign is not ended early, it might be justifiable in a situation of extremely low risk to continue to the end of a campaign. This would be when container closure, or product are not exposed to any increased contamination risk due to being far from the area of the problem. Then you should look at all the data and make a well-supported, risk-based decision.

Decontamination

17Q Has the FDA seen any new technology that looks promising for the decontamination/sterilization of barrier isolators? Or is hydrogen peroxide vapor the best choice at this juncture in the technologies' development?

17A Whatever works for you. There are other options, but we have not seen anything dramatically new recently.

18Q Is humidity and temperature mapping required for validating a VHP sterilized isolator where the product contact filling needle and stopper bowl are not VHP sterilized?

18A Temperature mapping in and out of the isolator is still important, controlling room temperature as well as knowing the dew point is important as well. Firm may not need rigorous mapping of humidity levels.

19Q What are the FDA's expectations regarding treatment of stopper bowls in place with VPHP?

19A There are lots of scenarios (sterilize out of place and aseptically install, sterilize in place). A firm should show the ≥6-log reduction and the FDA will evaluate it with supporting data.

20Q Does the Agency expect the crimping station to be VHP sterilized in an isolator system that VHP sterilizes the filling and stoppering station? (The crimping station is separated by a mousehole to the filling and stoppering section).

20A No to crimping station, but the FDA recommends to routinely perform manual sporicidal disinfection, not necessarily VHP. Separation between crimping station and main isolator's egress mousehole is important.

21Q How often do you recommend revalidating barriers with BIs?

21A "Knowledge is power" – while the FDA does not specify periodicity, it is important to have the data. Certainly, perform a BI challenge if there has been a change in the isolator to warrant concern.

22Q Are penetration studies necessary during continuing (on-going) validation studies? Are initial validation penetration studies sufficient?

22A To answer this question, we need clarity on whether this is penetration through media bags or into product vials.

Regarding media bags or plates, contract management needs attention. Your supplier agreement needs to tell you about penetration of chemical agent to the load. It may be prudent to do repeat testing every few years to periodically verify. Also you're only as good as the ability of your vendor to avoid unanticipated change (i.e., your agreements should include provisions for contractors to inform you proactively).

23Q Do you require VHP concentration (ppm) as a parameter for an acceptable decontamination cycle? How do you recommend the limits be set during validation studies or from process data? Do you want to see a minimum level only or a maximum level as well?

23A The FDA wants to see chemical concentration measurement during validation, and they strongly recommend you measure concentration during routine decontamination. This is analogous to other sterilization processes to assure that you have enough concentration to provide

surface decontamination. The generator tells you what initially exits the generator, but not what is inside the isolator. You should measure in at least one isolator location. To demonstrate the need, one company had a hole in the delivery tubing and did not detect the situation (i.e., reduced hydrogen peroxide was making it into the isolator) for a month. It was eventually discovered during re-qualification. Peroxide level and limits should be established during validation. The NIR measurement systems provide pretty good accuracy, and even if they might be to some extent "precisely inaccurate," the data still reveals meaningful fluctuations or abnormally low concentration levels.

Qualification

24Q What is the Agency's position on the use of vendor testing/Factory Acceptance testing rather than traditional qualification approaches?

24A Be flexible, one can't use FAT for OQ/PQ, but can be leveraged for IQ.

Transfer Systems

25Q If a transfer isolator is undocked, powered down, and moved to a clean unload area to load sterilized materials that are in containers, does the transfer isolator require battery power to keep the HEPA system on?

25A Possibly, but we really need more information to answer. Does turning the HEPA system off and on hurt the situation? If vials are sealed and chamber stays positive, then that's major risk mitigation so it could be feasible depending on the application.

26Q Is the introduction of materials (non-product contact such as sterilized parts bags) into a RABS of the same interest as into an isolator?

26A Yes it is, material introduction into isolators would seem to be of similar significance as material introduction into RABS. Advanced approaches, including the incremental improvement that can be provided by a good RABS design approach, warrants use of advanced transfer technologies when possible.

27Q What trends do you see to manage risk for decontaminating/sterilizing incoming material (e.g., syringe tubs) coming in to barrier isolators? How do you view effectiveness of different methods (manual wipe down, VHP, UV, and electron beam)?

27A VHP has been a common decontamination method for syringe tubs. UV is considered marginal. Bioburden on syringe tub is important, and is affected by how it has been handled, where the exterior bag opened, whether and how long it is exposed to the cleanroom environment – all these factors affect the predicted bioburden. Ebeam is mentioned, and is more often used in Europe to sterilize the outside of the tubs, but the FDA does not have much experience with ebeam in this application.

General

28Q Is the aseptic processing guidance being rewritten? What is the expected issuance date? Will there be any changes in the glove integrity test section?

28A The FDA aseptic processing guidance was issued in September 2004, and has been very well received as it is flexible in its discussion of design and encourages modern approaches! The Agency can get any related issues out on the FDA's Q&A Web site (formerly Human Drug cGMP Notes). Further explication of regulatory relief for media fills in isolators may be one area.

29Q What is your recommendation of room classification for Sterility Isolator Testing?

29A This is your choice. Usually, we see controlled unclassified background in a clean, orderly room. A firm would likely exclude blaming the background environment should a positive result occur (as the thought is that the background environment is not of consequence).

30Q For blow fill seal machines, is a Grade 'C' (Class 10,000) environment a mandatory requirement?

30A Aseptic guidance states with proper design Class 100,000 surrounding classification can be justified. Older designs need Class 10,000.

About the Panelists

Richard L. Friedman, M.S., is Director, Division of Manufacturing and Product Quality (HFD-320), Center for Drug Evaluation and Research/Office of Compliance. He can be reached by telephone at 301-827-9036 or by e-mail at rick.friedman@fda.hhs.gov.

Robert Sausville is Director, Division of Case Management, OCBQ, CBER, FDA. He can be reached by telephone at 301-827-6201 or by e-mail at robert.sausville@fda.hhs.gov.

Exclusive On-Line Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

International

The Global Harmonization Task Force (GHTF)[1] **has issued draft guidelines for comments on:**

- Regulatory Auditing of Quality Management Systems of Medical Device Manufacturers – Part 3: Regulatory Audit Reports
- Role of Standards in the Assessment of Medical Devices (revised)

Australia/ New Zealand

Added to the **Therapeutic Goods Administration (TGA)** Web site[2] in December 2006/January 2007 was:

- EU guidelines adopted now include Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/49348/2005). This guideline addresses the requirements regarding manufacturing processes, the comparability exercise for quality, considering the choice of reference product, analytical methods, physicochemical characterization, biological activity, purity, and specifications of the similar biological medicinal product.
- TGA has published[3] a new version of its guidelines relating to Good Manufacturing Practice (GMP) clearance for therapeutic goods manufactured outside of Australia. The guidelines state that the TGA will no longer automatically accept GMP certification from Pharmaceutical Inspection Cooperation Scheme (PIC/S) member countries, unless they are also Mutual Recognition Agreement (MRA) partners with Australia.

In January 2007, the **Australia New Zealand Therapeutic Goods Authority (ANZTPA)**[4] published on its Web site a 'Questions and Answers' page on GMP procedures under the merged authority.

Canada

Health Canada[5] has issued guidance on information to be provided to manufacturers for the reprocessing and sterilization of reusable medical devices. This draft guidance document is intended to assist manufacturers in understanding and complying with the regulatory requirements of section 21(1)(i) of the *Medical Devices Regulations* as they pertain to the directions for use for reusable medical devices.

Europe

The European Council and Parliament[6] have approved *Reach*, the proposed chemicals regulation on the registration, evaluation, and authorization of chemicals. The regulation will enter into force progressively from June 2007, and it is estimated that the registration process will take 11 years to complete.

Reported on the Web site for the **European Medicines Agency (EMEA)**[7] in December 2006 and January 2007 were:

- The European Medicines Agency has launched a new public database designed to facilitate access to information about medicines available in the European Union. The database can be accessed at www.eudrapharm.eu.
- Updated Scientific Data Requirements for the Plasma Master File (PMF) (Effective as of 1 June 2007)
- Updated ICH Topic Q3A (R2) - Note for Guidance on Impurities Testing: Impurities in New Drug Substances

The **Committee for Medicinal Products for Human Use (CHMP)** monthly report[8] from the December Plenary meeting held 11 to14 December 2006.

Documents prepared by the Biologics Working Party shown below were adopted at the December meeting:

- Overview of comments on guideline on the Scientific DATA requirements for a Plasma Master File (EMEA/CHMP/427732/2006).
- Draft Guideline on Environmental Risk Assessments for Medicinal Products Consisting of or Containing Genetically Modified Organisms (GMOs) (EMEA/CHMP/BWP/473191/2006).
- Overview of comments received on Draft Guideline on Environmental Risk Assessments for Medicinal Products Consisting of or Containing Genetically Modified Organisms (GMOs) (EMEA/CHMP/BWP/480303/2006).
- Concept paper on revision of the Guideline on plasma-derived medicinal products (EMEA/CHMP/BWP/495530/2006).

The **Heads of Agencies**[9] Web site has been updated with reports from the CMD(h) meetings held 13 to15 November 2006 and 11 to 12 December 2006.

An updated Question and Answer document on Mutual Recognition Procedures following the January 2007 EU enlargement was made available on the Web site at the beginning of January.

The **European Commission DG Enterprise**[10] announces a revision to GMP Annex 3 "Manufacture of Radiopharmaceuticals." This draft revision for public consultation is proposed in the light of new GMP requirements for active substances used as starting materials. It specifies application of Part II for the manufacture of radiopharmaceuticals. Comments are requested by 30 March 2007.

The **European Directorate for the Quality of Medicines (EDQM)**[11] is now the **European Directorate for the Quality of Medicines and Healthcare (EDQM and Healthcare)**. Its Web site[5] (updated December 2006) advertises the availability of European Pharmacopoeia Supplement 5.8, style guide, and structure nomenclature guide.

Ireland

IMB have published on its Web site[12] in December 2006, a summary of the responses to their public consultation into dual labelling of parallel imported

products. Some individual issues are addressed in the form of a Q&A session. At the same time, they announced that downloads from its Information Day 2006 – Manufacturing sessions are now available from the same Web site. Subjects include implications of new manufacturing legislation, sterile manufacture, reference and retention samples, engineering inspections, deviations, process quality review, and EMEA reflection document, Storage of Medicinal Products, Market Compliance, and Upcoming Regulatory Compliance Inspections.

Sweden

A new Swedish rule[6] on activities related to the handling of blood and blood components entered into force on 30 October 2006. The new provision implements all current European Union regulations on blood and blood components that are used as raw materials in the manufacture of medicinal products. It describes in detail how the gathering, control, and manufacturing of blood and blood components should be performed.

References

1. http://www.ghtf.org/
2. TGA - http://www.tga.gov.au/media/index.htm
3. RAJ Pharma ,Vol. 17, No. 12, December 2006.
4. ANZTPA - http://www.anztpa.org/index.htm
5. TPD - http://www.hc-sc.gc.ca/dhp-mps/prodpharma/index_e.html
6. RAJ Pharma, Vol. 18, No. 1, January 2007.
7. EMEA - http://www.emea.eu.int/whatsnewp.htm
8. EMEA - http://www.emea.eu.int/PressOffice/presshome.htm
9. HOA - http://heads.medagencies.org/
10. EC - http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm
11. EDQM - http://www.pheur.org/
12. IMB - http://www.imb.ie/

This information was provided by Peter Hagger, Pharmaceutical Research Associates (UK).

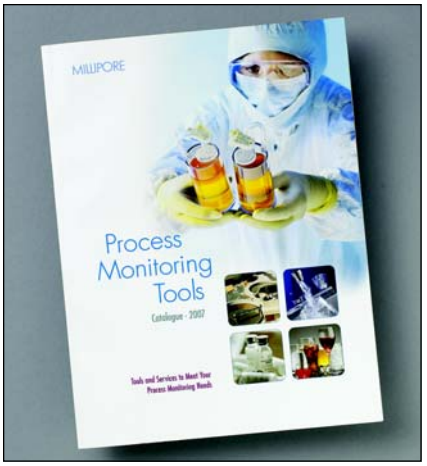
Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Water Treatment

Christ Water Technology Group has available their newest innovation called the Hydrokat. This catalytic exhaust-gas converter protects electrochemical processes from possible damage resulting from the explosion of gas mixtures. Its heart is a catalytic combustion element with automatic oxygen supply and integrated temperature regulation, making it capable of converting hydrogen-oxygen mixtures with any relative concentrations of the two gases.

Christ Water Technology Group, www.christwater.com.

Process Monitoring Catalog



Millipore Corp. has available its new product catalog highlighting tools and services to meet your process monitoring needs. The 92-page color catalogue (CA1002EN00) showcases Millipore's effective and reliable products that test for liquid and airborne contaminants, including systems, media, methods, validation protocols, and rapid detection tools for time sensitive applications.

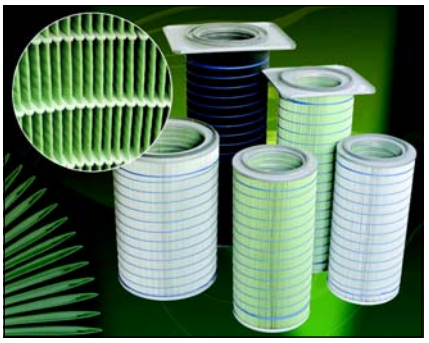
Millipore Corp., www.millipore.com.

Glove-Port

Extract Technology recently launched PharmaPort(PatentPending), a contamination-free glove-port interface for the company's renowned isolator range currently in widespread use throughout the pharmaceutical and aseptic processing industries. This new design will help to eradicate contamination hang-up around the operator access glove/gauntlet and the glazing/window panel, while improving operator safety by way of mechanically clamping the glove to the port.

Extract Technology Ltd., www. extract-technology.com.

Dust Collector



A full line of HemiPleat™ retrofit cartridges from Farr Air Pollution Control may be used to upgrade performance or solve problems of existing dust collector systems. The key to enhanced performance is a patent-pending pleating technology that opens up the pleats uniformly for more effective cleaning and better airflow. This filtration upgrade can greatly extend service life and reduce pressure drop compared to competitive dust collector cartridge filters.

Farr Air Pollution Control, www. farrapc.com.

Tubing

Now available from NewAge Industries are two types of polyethylene tubing: linear low density formula and a style co-extruded with Ethylene Vinyl Acetate (EVA). While both are made from non-toxic ingredients conforming to FDA standards, they offer different performance characteristics. Uses include air lines, chemical and fluid transfer, food and beverage processing and distribution, pharmaceutical processing, pneumatics and instrumentation, potable water, deionized water, wire jacketing, laboratory applications, and decorative coverings.

NewAge Industries, www. newageindustries.com.

Temperature Sensor

Weed Instrument has a new, novel-design sensor for temperature measurement in sanitary applications. The sensor (Weed Instrument Model #3142B) is especially beneficial where wipers or mixers can interfere with an inserted probe or thermowell. The sensor, attached inside a welding spud via a CIP sanitary clamp, is easily removed without need to disturb the mounting hardware, thus simplifying cleaning, replacing, and calibrating operations.

Weed Instrument Co., www. weedinstrument.com.

Containment Valve System

L. B. Bohle LLC has a new containment valve suitable for operation in areas where Operator Exposure Levels are limited and high containment operations are essential. The compact new valve is designed in two sections, active and passive, and is air operated using only a single actuator. Centering bolts ensure proper alignment while vacuum sealing and a connection to the dust collection system guarantees complete containment and increased operator safety.

L. B. Bohle LLC, www.lbbohle.com.

Peristaltic Pump

Precision dispensing of shear sensitive pharmaceuticals, biopharmaceuticals, and cell products by Flexicon peristaltic pumps, available from Flexicon America Inc., assures laboratories and manufacturers of gentle handling, closed fluid path sterility, precision dispensing accuracy and flexibility, and speed in meeting production economies. The closed fluid path that characterizes the peristaltic pumping process assures that sterile product never comes in direct contact with any moving parts before being dispensed.

Flexicon America Inc., www.flexiconamerica.com.

Software for Asset Information

Emerson Process Management has available Version 2.5 of its AMS™ Suite: Asset Portal™ software, which expands asset management capabilities. AMS Asset Portal Version 2.5 allows users to customize enterprise-wide asset information, including filtering and reporting alerts, polling on demand, and viewing graphical asset health reports. AMS Asset Portal is a Web-based tool that enables maintenance management personnel to obtain timely information to quickly identify critical equipment that is not performing and predict unexpected failures or off-spec product in time to take corrective action.

Emerson Process Management, www.emersonprocess.com.

Automation Platform for Cell Culture

Thermo Fisher Scientific Inc. has available its new Thermo Scientific Cell Growth and Discovery (CGD) WorkCell™, a fully enclosed, environmentally controlled automation solution designed for high capacity cell growth, supply, and in-line image analysis. Combining state-of–the-art software with sophisticated robotics, the CGD WorkCell is a turn-key system which can simultaneously handle multiple plate/flask formats and perform cell maintenance, colony selection, and RNAi studies.

Thermo Fisher Scientific Inc., www.thermofisher.com.

Peristaltic Pumps

Watson-Marlow Bredel will showcase its biopharmaceutical processing solutions, which include the 520, 620, and 720 Series of peristaltic pumps at INTERPHEX*2007* from 24 to 26 April 2007 at the Jacob K. Javits Convention Center in New York, New York, USA. The 520/620/720 family of peristaltic pumps are designed for the accurate metering, dosing, and transferring of sensitive fluids in sanitary environments, making them ideal for accurate filtration, fermentation, dispensing, coating, and seamless integration into reusable or disposable of bioprocess applications.

Watson-Marlow Bredel, www.watson-marlow.com.

Air Sampler

Coriolis® µ by Bertin Technologies is an air sampler that captures biological particles such as bacteria, fungi, and pollen. Its patented cyclonic technology delivers a liquid sample compatible with all analyses, including immuno-assay, PCR, flow cytometry, and microbiology. Coriolis® µ is a solution to collect a large panel of microorganisms (particle size >0.5µm) with a collection time or air flow rate up to 300L/min.

Bertin Technologies, www.bertin.fr.

Plant Asset Management

Honeywell has an enhanced version of its Field Device Manager, a key component of the company's plant asset management portfolio. Field Device Manager R301 is the first system to support both the latest Electronic Device Description Language and Field Device

Tool with Device Type Manager technologies without the use of conversion tools or add-on devices. This provides customers the broadest choice of instrumentation and valves to integrate with their distributed control systems and asset management systems to improve plant uptime and reduce maintenance costs.

Honeywell International, www.honeywell.com.

Visual Supervisors

Eurotherm has recently launched the new Eycon series of visual supervisors. These visual supervisors provide multifunction control, recording, and visualization. Eurotherm has a long history of experience in the control, data acquisition, and process automation market and now the Eycon Series brings that expertise into a single process unit.

Eurotherm, www.eurotherm.com.

Software for Submission of Medical Device Reports

Sparta Systems, Inc. has released its Beta version of the TrackWise eMDR Submission Manager™ software. The add-on software enables medical device companies to electronically submit Medical Device Reports (MDRs) to the US FDA. TrackWise eMDR Submission Manager™ enables device companies to effectively manage complaints and investigations, assess potential adverse events for safety risk problems, and comply with health authority reporting requirements, including those of the US FDA.

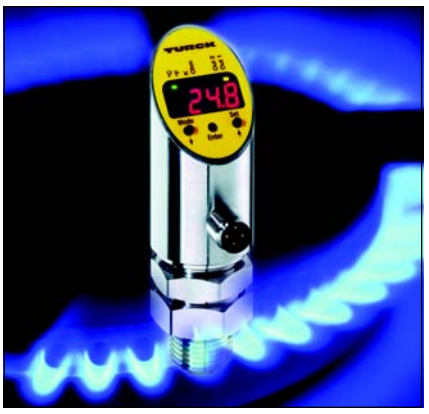
Sparta Systems Inc., www.spartasystems.com.

Vessel Outlet Valves

Fluid Transfer's Sanitary Flush-Bottom "Fluid Flow" Valves are uniquely designed to be welded flush with the bottom of vessels, thus eliminating any dead space between the valve and the vessel, so all product can be completely processed. These valves come in sizes from 1-1/2" to 4" and can be automated with either pneumatic or electric actuators. The maximum working pressure is 450 PSIG at temperatures to 300° F.

Lee Industries, Inc., www.leeind.com.

Temperature Sensors



TURCK introduces a line of highly reliable and easy to program temperature sensors. The TS400 and TS500 temperature sensors incorporate a multitude of design features that make the sensors suitable for nearly all factory and process automation applications. TS400 and TS500 temperature sensors are platinum resistance temperature detectors, a technology commonly referred to as Pt-100.

TURCK, www.turck.com.

Pressure/Flow Transmitter

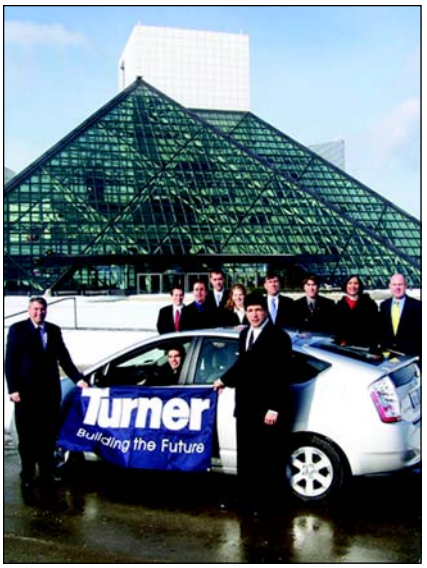
A FOUNDATION Fieldbus version of the Yokogawa EJX910A multivariable pressure/flow transmitter, along with a flow configuration tool using FDT/DTM technology based software, is now available from Yokogawa Europe. The patented DPharp single-crystal silicon resonant sensor technology ensures high accuracy, provides superior overpressure protection, minimizes the effect of temperature and static pressure changes, and provides a unique multisensing capability.

Yokogawa Electric Corp., www.yokogawa.com.

To submit material for publication in ***Pharmaceutical Engineering****'s New Products and Literature department, e-mail press releases with photos to* ***pharmeng@ispe.org*** *for consideration.*

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Turner Employees Earn LEED Certification, Chance to Win Car



Joseph Schilens, a project superintendent in Turner Construction's Cleveland office, was one of 250 Turner employees to become Leadership in Energy and Environmental Design (LEED) certified in 2006. All Turner employees who were LEED accredited as of 31 December 2006 were entered into a lottery to receive the use of a 2007 Toyota Prius hybrid as their company-provided vehicle for three years. Joseph Schilens was selected as the winner of the 2007 Toyota Prius.

Turner Construction, www.turnerconstruction.com.

Korsch and Thomas Engineering Announce Partnership

Korsch AG and Thomas Engineering Inc. (TEI) have formed a strategic global partnership that will enable the global distribution of leading edge technology for coating pans, tablet presses, and press tooling, while permitting their multinational customers to standardize on critical process equipment across global sites. TEI will work jointly with Korsch America to promote, sell, and support Korsch equipment in North America. Thomas Engineering will no longer sell new Manesty Tablet Presses; however, all existing Manesty customers will continue to be fully supported with regard to technical service and spare parts.

Korsch AG, www.korschamerica.com.

Thomas Engineering Inc., www.thomaseng.com.

Nicomac Partners with ICOS Impianti Spa

Nicomac Inc. has partnered with ICOS Impianti Spa for marketing and servicing the entire ICOS line of products for the pharmaceutical industry. In addition to well established products such as autoclaves, dry heat sterilizers, and stopper processors, Nicomac will promote and provide after sales services in the US, Canada, and Puerto Rico for ICOS products.

Nicomac Inc., www.nicomac.com.

Icos Impianti Spa, www.icosimpianti.com.

Rockwell Automation Acquires ProsCon Holdings

Rockwell Automation Inc. has acquired ProsCon Holdings Ltd., a privately held engineering firm offering proven and technically unique design solutions to the process industry. Areas of expertise include process technology, control systems, and information technology. ProsCon also provides modular solutions as an innovative and cost-effective approach delivering faster implementation of new facilities, as well as retrofits for existing plants.

Rockwell Automation Inc., www.rockwellautomation.com.

ProsCon Holdings Ltd., www.proscon.ie.

Sartorius Combines its Biotech Division with Stedim

Sartorius AG has signed a binding agreement with Stedim Biosystems SA and its founders thereby acquiring the control of Stedim. Sartorius will combine its Biotechnology Division with Stedim to create a globally leading technology provider for the biopharmaceutical industry. The combined company, to be named "Sartorius Stedim Biotech SA" will be listed on the Paris stock exchange. The founders and majority shareholders of Stedim support the transaction and will stay invested in the combined company.

Sartorius AG, www.sartorius.com.

Stedim Biosystems S.A., www.stedim.com.

Werum Software and Systems Receives Award

Werum Software and Systems is the recipient of the 2007 Frost and Sullivan Company of the Year Award in the Manufacturing Execution Systems category for the pharmaceutical and biopharmaceutical industries. Each year, Frost and Sullivan presents this award to the company that has demonstrated excellence in business development, competitive strategy, consistent growth, and leadership. The award also recognizes Werum's continuing innovation and its commitment to customer satisfaction in the pharmaceutical industry.

Werum Software and Systems, www.werum-america.com.

*To submit material for publication in **Pharmaceutical Engineering**'s Industry and People department, e-mail press releases with photos to **pharmeng@ispe.org** for consideration.*

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

ISPE Student Chapter Profile: Campbell University

by Daniel Shin, PhD, Faculty Advisor, ISPE Student Chapter, Campbell University, and Martin Rock, President, ISPE Carolina-South Atlantic (CASA) Chapter

Editor's Note: One of ISPE's goals is to develop students into competent pharmaceutical professionals and encourage them to pursue careers in the industry. ISPE Student Chapters play an important role in this endeavor. This article is the first in a series profiling ISPE Student Chapters and the people, education, research, and activities of tomorrow's pharmaceutical professionals.

Getting Started

In December 1995, Jane Brown, then first chair of the Student Affairs Committee of the ISPE CASA Chapter, contacted Mark Yates, PhD, then a faculty member at Campbell University in North Carolina, USA. Brown wanted to know whether Yates was interested in starting a Student Chapter at Campbell and serving as faculty advisor.

Yates was involved in initiating the Bachelor of Science program in pharmaceutical sciences within the School of Pharmacy at Campbell. But, a year later, he accepted the challenge of starting the ISPE Student Chapter at Campbell University. The first Student Chapter kickoff meeting at Campbell University was held in the spring of 1996 with seven students.

Brown currently serves as Chairman of the International Board of Directors of ISPE and is still actively involved with the CASA Chapter Student Development Committee. Yates, currently employed with Wyeth Pharmaceuticals, is also still involved with the CASA Chapter Student Development Committee.

Shin (second from left) with Campbell students at the 2006 ISPE Student Leadership Forum.

Growing the Chapter

The ISPE Student Chapter at Campbell was the first Student Chapter to send students to an ISPE Annual Meeting (New Orleans – 1998). So far, four Campbell students have won the local student poster competition at the CASA Chapter level, all of whom participated in the international poster competition at ISPE Annual Meetings.

To date, two international poster champions were members of the Campbell Student Chapter. Eric Blaesing won the undergraduate poster award in 2003 and Wendy Haines, PhD, while a graduate student at UNC – Chapel Hill, won the graduate level poster award in 2001. Haines now serves as the Chair of the CASA Student Affairs Committee.

After Yates left Campbell University in 2000, the activities of the Student Chapter slowed down due to the lack of a faculty advisor. Daniel Shin, PhD, joined the Department of Pharmaceutical Sciences at Campbell University in the fall of 2001, and a year later, agreed to serve as a faculty advisor to the Student Chapter.

Shin made a plan to recruit new student members and organize the student leadership. He has contacted some professors within and outside of the Department to get a few minutes of their class time to introduce ISPE.

Yates, who became the Student Chapter's industry advisor, and many other members in the ISPE CASA Chapter leadership, helped recruit featured speakers for the Student Chapter's monthly meetings. Many local leaders gave presentations at those meetings.

Campbell University students get a firm grip on the dos and don'ts of networking from Bo Crouse-Feuerhelm, Past Chairman of the ISPE Student Development Committee.

The local CASA members were very helpful and enthusiastic about coming to Campbell and speaking to the students. Since Campbell is located in a rural area, these guest speakers sacrificed their precious time and gas money to drive out to the campus in the evening to help the students understand what pharmaceutical scientists and professionals do in the real world.

There was no explosive growth of membership at Campbell; rather it was a gradual steady increase. The ISPE student membership at Campbell has grown from seven students in 1996 to 60 active students in 2006. Most of them are majors in pharmaceutical sciences, but there are some pharmacy students, clinical research, and other science majors. Last year, the Student Chapter at Campbell University was the recipient of the first ISPE Student Chapter of the Year Award.

Let's Meet

Networking opportunities are one of the great benefits of being an ISPE

Concludes on page 2.

ISPE Student Chapter Profile: Campbell University

Continued from page 1.

A student gets information about ISPE and its Student Chapter during a High School Career Fair held at Campbell University.

Student Member. There is always a warm and friendly atmosphere at various ISPE functions and meetings, including conferences, seminars, technology shows, career fairs, and student leadership forum meetings. Shin encouraged students to attend these functions since they were sure to learn more about the industry and career opportunities through exposure at these meetings.

Virtually all of the students who attended ISPE events said that they were excellent because they were great opportunities to see a part of the real world and interact with industry professionals. The students are interested in attending as many of these activities as possible even though they are under severe time constraints pursuing their academic goals.

Most of the meetings are open to the students at reduced prices or even free of charge. The financial support provided by the ISPE CASA Chapter to the Student Chapters is also helpful to the students. Yearly monetary support, reduced annual fees, and free admission to conferences, seminars, technology shows, etc., all help to encourage student participation.

Another benefit to students is that ISPE Members, both on a local and national level, are proactive in helping the students prepare and enhance their resumes and their interviewing skills. Seminar sessions are held on internships, getting a job, poster competitions, etc. Many of the graduates from these programs have landed jobs through ISPE at various industrial companies, including Biogen Idec, Novo Nordisk, Talecris, GSK, Eli Lilly, Wyeth, D&Z, CRB, Monsanto, Magellan/Cardinal, EISAI, AAI Pharma, and others.

The ISPE Difference

There are many other organizations available to students in the pharmaceutical field. But, ISPE is the only organization that supports students with this depth and breadth of industry interaction. Student initiatives are truly a wise investment by ISPE and by the profession since the students represent our future.

Many students who have benefited from ISPE membership as students, and have graduated from their universities, now serve in various voluntary capacities for ISPE. These students are testimony to the on-going mutual benefits of the student programs for both students and ISPE.

The spirit of volunteerism and dedication among the ISPE industry members is priceless and contagious. The atmosphere created by this infectious spirit of goodwill among the members is very inviting to the students and makes everyone feel welcome. The students learn from the devotion and service of the industry members, and many of these students go on to reciprocate when they are in industry positions.

Now, there is a very positive momentum at work at Campbell University. The Campbell students who joined ISPE clearly see the opportunities provided by ISPE membership. Each student member then becomes an advocate for the ISPE organization. Through word of mouth promotion among the students themselves, many other students have joined ISPE. As result of this positive momentum, it takes much less effort now to sustain the student chapter.

For more information on the research Student Members are involved in at Campbell, visit www.ispe.org.

April Paris Conference Highlights Nano and Micro Technology, and More

ISPE will hold its Paris Conference 16 to 19 April at the Hilton Hotel with industry leaders presenting eight seminars on:

- Revision of the GAMP® Good Practice Guide: Validation of Process Control Systems
- Nano and Micro Technology for Pharmaceutical Products and Processes
- Process Analytical Technology (PAT)
- Pharmaceutical Water, Regulation, and Innovation
- Facility of the Year Exposé
- Biosafety
- Design Space
- Project Management – Facing Today's Challenges

For more information and to register, please go to www.ispe.org/ParisConference.

Washington Conference Highlights Facilities Summit and FDA Collaboration

Technical Documents and 16th Barrier Isolation Forum Take Spotlight

ISPE will feature four exciting highlights in addition to many other opportunities for pharmaceutical manufacturing professionals at the ISPE Washington Conference to be held 4 to 7 June 2007 at the Crystal Gateway Marriott in Arlington, Virginia, USA.

Facilities Summit

As the international expert on pharmaceutical facilities, ISPE will offer presentations and innovative case studies from leaders in the field. Panel discussions will include Facility of the Year 2007 Category Winners with virtual facility tours.

This multi-day, multi-track program, to take place 4 to 5 June, will include content in three key areas, Project Delivery, Regulatory, and Manufacturing Technology/Operations. Spotlighting case studies and state-of-the-art facilities, interactive discussions will focus on practical solutions to facility design (new or renovated), construction, building green, and qualification for operational excellence.

The Summit also will feature the most up-to-date information on the Facility of the Year Awards, bringing the engineers and architects who designed those state of the art facilities, together to share their insights with participants.

FDA-ISPE Collaboration

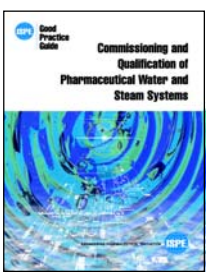
ISPE and the US FDA are co-sponsoring a series of first-ever interactive seminars designed to allow delegates to impact their own futures by participating in the development of how ICH Q8, Q9, and ultimately Q10 guidelines will be implemented.

These sessions will focus on Product Quality Lifecycle Implementation (PQLI), and will be the foundational meetings for an open, continuous dialogue between industry stakeholders and regulators, ultimately helping to generate a pragmatic approach to implementing Q8, Q9, and Q10 regarding Quality by Design and Quality Systems.

Prominent US regulatory representatives will co-host this ground-breaking event, which also will comprise six breakout sessions for working groups to comment on and capture industry input.

New ISPE Technical Documents

The "Ready for Release," ISPE Good Practice Guide: Commissioning and Qualification of Pharmaceutical Water and Steam Systems seminar will be held 4 to 5 June.



This two-day seminar will explore the successes and failures of design, installation, qualification, continued operation, and maintenance of qualified water and steam systems through a series of regulatory updates and case studies. Participants will learn about the relationship between quality impact of the utilities and the business risk associated with their operation. Impact classification and release highlights of the *ISPE Good Practice Guide: Commissioning and Qualification of Pharmaceutical Water and Steam Systems* also will be discussed.

The "Ready for Release," Bulk Pharmaceutical Chemicals (BPC) Baseline® Guide, Review by Developers seminar will be held 4 to 5 June. The BPC Guide, originally published in June 1996, has been undergoing a complete revision. This session will allow an opportunity to interact with the authors and review the completed Guide revision with the executive committee members. Participants will hear from experts in the field to gain a real "hands-on" experience in the application of the Guide. With assistance from subject matter experts from the API Community of Practice, key changes and hot topics of the revised Guide will be presented and discussed.

Gold Standard in Barrier Isolation

ISPE will host the 16th Annual Barrier Isolation Technology Forum – the longest running Barrier Isolation Technology Forum in the world. ISPE's Barrier Isolation Technology Forum is the standard by which all others are measured, and continuously builds upon the foundation of knowledge and best practices set in place during previous years, providing a vital opportunity to gain updates and examine new case studies.

This program will feature the latest developments in Barrier Isolation Technology. It will include background information, technology updates, a series of new case studies, agency presentations, and industry comments. Offering a global perspective with speakers from Europe and the US, this seminar will present state-of-the-art advancements for use in developing and manufacturing pharmaceuticals utilizing Barrier Isolator Technology.

Participants will gain insight into updated technologies applicable to advanced aseptic processing using Barrier Isolation; learn "what not to do" from those who've done it; participate in peer discussion groups that will answer your own questions on Barrier Isolation Technology issues; and identify regulatory agency perspectives that will streamline your regulatory submission/approval process.

For more information about, or to register for, the Washington Conference, please visit www.ispe.org/washingtonconference.

ENGINEERING PHARMACEUTICAL INNOVATION ISPE

Mark Your Calendar with these ISPE Events

April 2007

5	Central Canada Chapter, Student Poster Competition, Montreal, Quebec, Canada
5 - 6	Japan Affiliate, Annual Meeting, Tower Hal, Tokyo, Japan
10	San Diego Chapter, New Member Breakfast, San Diego, California, USA
11	New Jersey Chapter, Dual Track Sessions, Session Topics: Error Reduction—the Human Factors and Cleaning Validation, Holiday Inn, Somerset, New Jersey, USA
12	Greater Los Angeles Chapter, Watson Laboratories Tour/Training, Corona, California, USA
12	South Central Chapter, Education, Exhibits, and PPG Industries Plant Tour, Houston, Texas, USA
13	Central Canada Chapter, Networking Event, Toronto, Ontario, Canada
13	Czech Republic/Slovakia Affiliate, Risk Analysis Workshop
13	Delaware Valley Chapter, Habitat for Humanity, Pennsylvania, USA
14	Puerto Rico Chapter, Student Leadership Forum, Puerto Rico
16	Delaware Valley Chapter, Meeting and Student Poster Judging, held in conjunction with the ISPE Philadelphia Training Series, Philadelphia, Pennsylvania, USA
16-19	**Philadelphia Classroom Training, Hilton Philadelphia, Philadelphia, Pennsylvania, USA**
16-19	**Paris Conference, Hilton Hotel, Paris, France**
17	Boston Area Chapter, Seminar on Contract Manufacturing, USA
17	San Francisco/Bay Area Chapter, Commuter Conference, Primary Systems Panel, USA
18	Nordic Affiliate, Event: How to Minimize Cleaning Validation, Copenhagen, Denmark
19	Ireland Affiliate, Training Seminar (half-day) and Gala Dinner, Dublin, Ireland
19	Puerto Rico Chapter, Biotechnology Track, Puerto Rico
24 - 25	Poland Affiliate, Conference on Innovations in the Pharmaceutical Industry, Starogard Gdanski, Poland
24 - 26	**INTERPHEX New York, Javits Convention Center, New York, New York, USA**
26	New Jersey Chapter, Student Poster Competition, Hoboken, New Jersey, USA
26	San Diego Chapter, Dinner Meeting, La Jolla, California, USA
30	DACH Affiliate, Process Analytical Technology COP Meeting, Frankfurt, Germany

May 2007

2	Midwest Chapter, Extended Education and Vendor Day with Bayer Plant Tour, Sheraton Overland Park Hotel, Overland Park, Kansas, USA
3	Central Canada Chapter, Education and Networking, Quebec City, Quebec, Canada
5	Puerto Rico Chapter, Annual Golf Tournament, Puerto Rico
7	Carolina-South Atlantic Chapter, Bausch & Lomb Facility Tour, Fuquay Varina, North Carolina, USA
7	Delaware Valley Chapter, Golf Outing, Philmont Country Club, Philadelphia, Pennsylvania, USA
7 - 8	ISPE Singapore Training Course - Cleaning Validation, Singapore
7 - 10	**Barcelona Classroom Training, Renaissance Barcelona Hotel, Barcelona, Spain**
9	New Jersey Chapter, Golf Outing, Farmstead Country Club, Lafayette, New Jersey, USA
10	Italy Affiliate, Colleretto Giacosa, Biotechnology Manufacturing, Turin, Italy
10	Nordic Affiliate, Clean Utility - Purified Water and WFI, Stockholm, Sweden
10 - 11	DACH Affiliate, Workshop, Theme: "Neubau Feststofffabrik/Prozessanlagen/Diagnostika/Medizinprodukte," Graz, Austria
11	Ireland Affiliate, Abbott Plant Tour and Golf Outing, Sligo, Ireland
15	Boston Area Chapter, Seminar on Product Contact Materials, USA
15	Central Canada Chapter, Toronto Breakfast Seminar, Toronto, Ontario, Canada
17	Central Canada Chapter, Montreal Breakfast Seminar, Montreal, Quebec, Canada
17	New Jersey Chapter, Cardinal Health Tour, Somerset, New Jersey, USA
17	San Francisco/Bay Area Chapter, Dinner Meeting, California, USA
21 - 25	**ISPE and Society of Bioprocessing Professionals (SBP), 5th Annual Bioprocessing Institute, Hyatt Regency at Penn's Landing, Philadelphia, Pennsylvania, USA**
23	Argentina Affiliate, Masterly Conferences, cGMP for the 21st Century FDA Initiatives, Buenos Aires, Argentina
24	Belgium Affiliate, Technical Meeting on Disposables Technology, Brussels, Belgium
24	Puerto Rico Chapter, Project Management Program, Puerto Rico
24	San Diego Chapter, Dinner Meeting, La Jolla, California, USA

Dates and Topics are subject to change

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

ISPE, SBP Host 5th Annual Bioprocessing Institute 21 to 25 May

ISPE and the Society for Bioprocessing Professionals (SBP) will host the 5th Annual Bioprocessing Institute, a highly-regarded conference that will feature both introductory and advanced courses, with the opportunity to learn from and share insights with innovative biotechnology professionals. The conference will be held 21 to 25 May 2007 at the Hyatt Regency at Penn's Landing, Philadelphia, Pennsylvania, USA.

This conference will include nine courses with 18 workshops that will provide delegates with an immediate real life learning experience, including exhibits and plant tours.

Courses include:

- **Bioreactor Systems: Development, Design, and Operation**
  This course will help participants gain an understanding of the development, selection, design, validation, operation, and regulatory compliance of large scale bioreactor systems used for production of therapeutic proteins and related products.
- **Bioprocess Development and Scale-up for Fermentation and Cell Culture**
  In this advanced course, workshop teams will get involved in the decision-making process that's required to move fermentation and cell culture toward manufacturing for a commercial bioproduct.
- **Separation Technologies for Bioprocessing**
  This course will cover the separation technologies for downstream bioprocessing, including basic principles; cleaning methods; and problem-solving workshops focusing on the design of a protein purification process.
- **Bioprocess Development for Downstream Purification**
  This advanced workshop will focus on the points and tools to consider when developing a downstream purification process. Participants can improve their understanding of the basic biochemical process technology typically used in purification processes for proteins from recombinant hosts.
- **Scale-up of Bioprocessing Systems for Purification**
  In this advanced workshop, participants will acquire an understanding of approaches and tools used in the scale-up of chromatography and tangential flow filtration systems including pumping, piping, support equipment such as bubble traps, and instrumentation.
- **Application and Design of Bioprocessing Equipment**
  Participants will gain an understanding of the principles and component design details of the bioprocess equipment necessary for late stage phase III clinical trials for an FDA-approved drug.
- **Cleaning Technologies for Bioprocessing Systems**
  This course will cover cleaning technologies including Clean-in-Place (CIP). Participants will review the principles and practices of the application of CIP technology to bioprocess systems including considerations for compliance and validation.
- **Designing Facilities for Successful Bioprocessing Operations**
  This course will focus on the concepts of designing multi-purpose, multi-cellular cGMP biologics processing facilities as they are becoming more complex and challenging as new cell lines, global harmonization, and processing technologies are advancing.
- **Bioprocessing Overview**
  A series of non-workshop sessions focusing on:
  - Bioreactor Systems: Development, Design, and Operations
  - Separation Technologies for Bioprocessing Systems
  - Application and Design of Bioprocessing Equipment
  - Cleaning Technologies for Bioprocessing Systems

For more details and on-line registration, visit: http://www.bioprocessingprofessionals.org/Institute_InstituteCourses.htm

Philadelphia Training 16 to 19 April

ISPE Philadelphia Training will be held 16 to 19 April 2007, Hilton Philadelphia City Avenue, Philadelphia, Pennsylvania, USA. Courses taught by leading professionals in their fields include:

- HVAC for Pharmaceutical Facilities
- Cleaning Validation Principles
- Auditing for GMP
- Drug Manufacturing Facility Design
- Complying with Part 11 – Risk Management
- GMP Fundamentals for the Pharmaceutical Industry
- Basic Principles of Commissioning and Qualification
- Clinical Trial Materials

All courses will provide valuable information to take back and use in your job.

For more details on the courses and instructors, visit www.ispe.org/philadelphiatraining.

INTERPHEX*2007*: What to Expect and What's New

Keep pace with the rapidly evolving world of pharmaceutical and biotech manufacturing at INTERPHEX*2007*, where you can access the newest products from more than 1,000 exhibiting companies, learn about advanced solutions and innovative business practices, get expert perspectives from industry movers and shakers, and network with thousands of industry peers from across the country and around the world. INTERPHEX*2007* will be held 24 to 26 April at the Jacob K. Javits Convention Center in New York, New York, USA.

Show Hours:

Tuesday, 24 April, 10 to 5
Wednesday, 25 April 10 to 5
Thursday 26 April 10 to 3

Conference Hours:

Tuesday, 24 April, 9 to 4
Wednesday, 25 April 9 to 4
Thursday 26 April 9 to 3

Sponsored by ISPE, this event is the largest and most distinguished industry event taking place worldwide. See what you have in store:

- a comprehensive conference program offering views and opinions of industry leaders, as well as strategic and technical applications on topics focusing on IT, Biopharmaceutical, Facilities, Manufacturing, Outsourcing, Supply Chain and Security, Contamination Control, and Pilot Plants
- new and innovative products and service trends from more than 1,000 exhibitors within the pharmaceutical manufacturing industry
- the announcement and celebration of outstanding achievements in facility design and construction at the third annual Facility of the Year Awards
- networking with peers from across the country and around the world
- free daily keynotes by industry thought leaders and innovators
- technology pavilions focused on automation and packaging
- exclusive ISPE Member discounts on event registration fee – ISPE Members receive 20 percent off conference registration fees
- complimentary passes to the Exhibit Hall
- exclusive ISPE Member Lounge with complimentary continental breakfast, beverages, Internet access, and small meeting rooms

NEW Life Sciences Job Fair

Produced in partnership with ISPE and AAPS

The Life Sciences Job Fair will provide opportunities to meet representatives from a broad range of companies who have employment and career opportunities, including exhibitors and other suppliers, pharmaceutical and biotech companies, industry recruiters, and more.

ISPE Member Lounge and Life Sciences Job Fair Hours:

Tuesday, 24 April, 9 to 5
Wednesday, 25 April 9 to 5
Thursday 26 April 9 to 3

FOYA Finalists: Find Out at INTERPHEX

This year, Facility of the Year Awards (FOYA) Category Winners will be named at INTERPHEX*2007*.

Each Category Winner will be available to discuss their facility operation as well as offer virtual tours of their new facility during exhibit hours.

Award winners for each category and the overall Facility of the Year Award winner will receive high profile attention and media coverage from ISPE, INTERPHEX, and *Pharmaceutical Engineering* magazine including:

- all Category Winners receive crystal awards
- Facility of the Year Awards competition winner receives the prestigious crystal and marble award
- worldwide distribution of press releases to global media outlets detailing facilities of the Category Winners and Facility of the Year Awards winner
- recognition via announcements during keynote sessions and special displays at INTERPHEX and ISPE's 2007 Annual Meeting

ISPE Member Lounge Sponsors

Premier Tec-Ultra Clean Magnetic Mixer • Veolia Water Technologies
• Commissioning Agents •
AWS Bio-Pharma Technologies • Burkert Fluid Control Systems
• Compliant Logistics •

INTERPHEX*2007*: What to Expect and What's New

Continued.

- invitation to attend INTERPHEX Leadership Dinner with ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine leadership in New York
- media advisory sessions featuring Category Winners and Facility of the Year Awards competition winner during INTERPHEX and ISPE's Annual Meeting
- coverage in two Special Editions of *Pharmaceutical Engineering* magazine
- cover story in *Pharmaceutical Engineering* magazine and feature article in *Pharmaceutical Processing* magazine

Special Room Block at INTERPHEX*2007* for ISPE Members

At INTERPHEX*2007*, you can connect with other ISPE Members before and after the show! ISPE has a special room block for ISPE Members attending INTERPHEX*2007* at the Sheraton New York Hotel and Towers (811 7th Avenue).

The ISPE Member rate is $259 single/double. You can make your reservations through www.interphex.com and click to "travel/hotel."

To receive your discounted room rate:

1. Click on the travel desk homepage
2. Select "ISPE" from the "I am a" menu
3. Use pass code ISPE2007

ISPE Containment COP First General Meeting at INTERPHEX

ISPE's Containment Community of Practice (COP) is organizing its first general meeting on 24 April from 5:00 to 6:30 pm to be held in conjunction with the INTERPHEX Show at the Javits Convention Center. The program will include ice breaking activities, a short presentation, networking opportunities, and information about upcoming COP events. Light appetizers and beverages will be served. The event is open to all Containment COP members and will be free for all ISPE Members. Non-ISPE Members will have to pay a nominal $30 registration fee.

Here's a brief overview of all that's new and exciting at this year's show:

Two Visionary Keynotes

What's Next: Where Devices and Medicine Go From Here…

Tuesday, 24 April at 11:30 am

Bill Cook, Chair and CEO of the Cook Group Inc., will survey the challenges and potential presented by one of the life science industry's fastest-growing segments— the convergence of drug and device technologies. With his unique perspective of growing device and biotech companies, Mr. Cook explores the partnership strategies, innovative approaches to R&D, investment, and regulatory issues needed to create winning combination products that will transform healthcare.

Innovation, Integration, and Exploration: The Future of Life Science Industries

Wednesday, 25 April at 11:30 am

G. Steven Burrill, CEO of Burrill and Co, has championed the growth and prosperity of the biotechnology industry and life sciences industries for 40 years. One of the industry's original architects, he continues to be an industry leading expert and visionary. Building on this history, he will present statistics, predictions and visions for the future. Mr. Burrill will explore how scientific advances, technological convergence and expanding global markets will continue to transform the life sciences industries and open up new frontiers for personalization and commericialization.

NEW Co-Located Event!

Admission is FREE with your INTERPHEX badge.

PharmaMedDevice 2007 Conference and Exhibition

PharmaMedDevice™ is the first event to fully illuminate the convergence of the medical device, pharmaceutical, and biologic industries. This transformational event addresses the needs of the emerging combination product market and the exciting innovations taking place in drug delivery technology and healthcare today. PharmaMedDevice provides a dynamic platform for education, partnering, sourcing, and discovery of innovative new products – and provides a unique opportunity for cross-sector collaboration across these industries.

ISPE and the *Journal of Pharmaceutical Innovation* (JPI) are official Sponsors of PharmaMedDevice 2007.

BIO TO BUSINESS – *Bridging People, Opportunities, and Technologies*

It's a dynamic time for the biotechnology industry, and discoveries are occurring at a rapid pace. If you're a small- to medium-sized biotech company interested in scale-up production, INTERPHEX is a valuable resource for partnerships, networking, education, products, technologies, and services in both small and large molecule processing and production.

Concludes on page 8.

INTERPHEX*2007*: What to Expect and What's New

Continued from page 7.

NEW INTERPHEX/BioExecutive International Roundtable

Presented by INTERPHEX and BioExecutive International magazine
Wednesday, April 25, 8:00 am to 11:30 am – Invitation only

In the ever changing business environment, there is a growing necessity to strategically align, partner, and work with other entities to ensure the success of your future business. Key biopharmaceutical and pharmaceutical industry executives will discuss, debate, and provide insight on how their companies see the future in light of the current business environment.

NEW Bio/Techfunding Forum

Funding for Early Stage Life Sciences Companies

Presented by Life Sciences Greenhouse of Central PA
Thursday, 26 April, 10:00 am to 11:30 am

What kinds of funding are available to startup companies, when is each type appropriate, and how does one get connected to sources? What does each type of investor look for? What should a startup look for in an investor (i.e., what makes a good partner)? A panel of industry insiders, including representatives from federal funding sources, angel investors, venture capitalists, entrepreneurs and industry technology councils will explore the issues and provide practical answers.

NEW Educational Opportunities

With nearly 100 cutting-edge sessions led by respected industry experts, the INTERPHEX*2007* Conference is unsurpassed for up-to-the-minute, intensive education geared toward problem solving and productivity enhancement. New additions to this year's conference program include:

NEW Management Conference Track

These results-oriented sessions are designed to help you develop the critical management skills to stimulate and sustain innovation, maximize productivity, reduce waste and achieve manufacturing excellence. Whether you're looking to execute lean manufacturing techniques, achieve six sigma quality or create a culture of continuous improvement, you'll find the tools and strategies you need.

A STATE-OF-THE-ART Biotechnology Track

Sessions covering many of the most challenging issues in commercial scale bioprocessing, including disposables and single use technologies, prefilled syringes, cell rupture unit operation, direct oxygen injection in aerobic fermenters, and more serve the educational needs of the growing biotechnology audience at INTERPHEX.

NEW Supply Chain and Security Track

This new track provides a strong foundation in the fundamentals of RFID technology and its application to product authentification and supply chain security. Topics include 21st Century supply chain models, cold chain, supply chain risk, network critical infrastructure for RFID, removing risk from the pharmaceutical supply chain, transaction life cycle management and supply chain compliance, real world item level tagging and many others.

NEW RFID Master Class

Presented by the International RFID Business Association in collaboration with the RFID Technical Institute
Monday, 23 April, 8:00 am to 4:00 pm

Leveraging RFID, Sensor, and Wireless Technologies for Manufacturing Process Improvement and Supply Chain Efficiency

This concentrated, thought provoking class, created specifically for INTERPHEX*2007* attendees, provides a solid foundation in the latest developments in RFID technology and their practical application to the pharmaceutical manufacturing and the supply chain.

NEW ISA CAP Review Course

Three days, 23 to 25 April, 8:00 am to 4:00 pm / CEU credits: 2.1

This course reviews the Certified Automation Professional Job Analysis Domains, Tasks, Knowledge and Skill Areas, and Technical Topic areas developed as the basis for the CAP examination. It is designed specifically for experienced automation professionals preparing to take the exam. An explanation of the examination process, and sample test-taking questions are provided. Separate registration required.

NEW Package Design Showcase

Sponsored by Package Design magazine

See award winning package designs for pharmaceutical, cosmetic and medical device products that have been selected by respected industry organizations, and explore new design possibilities in the Package Design conference track. Sessions illustrate opportunities for pharmaceutical, cosmetic and medical device companies to strengthen their brands through effective package design and innovation.

Singapore Conference 10 to 12 June: Driving Regional Pharmaceutical Manufacturing Excellence

Held annually since 2000, the ISPE Singapore Conference offers a world-class educational and networking opportunity for pharmaceutical manufacturing professionals in Asia.

With a panel of 25 international and regional speakers, this is the only conference in Asia that addresses the latest regulatory, technological, and practical issues facing multinational and regional pharmaceutical manufacturers in API, secondary, and biotech manufacturing.

Key features of the 2007 ISPE Singapore Conference are:

- Six industry tracks and one Special Focus Track on Manufacturing Excellence tailored to address specific pharmaceutical manufacturing issues
- Two pre-Conference workshops providing in-depth knowledge of selected processes and procedures
- Pharma Nite – an opportunity to network and build relationships with the international and regional speakers and delegates to the Conference
- Educational plant tours – a unique opportunity to visit some of the most advanced pharmaceutical manufacturing plants in Asia. Registered delegates can choose to visit any one of the following pharmaceutical manufacturing plants in Singapore on a space-available basis – Pfizer; Novartis; Schering-Plough; Merck, Sharp and Dohme and GlaxoSmithKline
- Facility of the Year Award Category Winners – this Award recognizes state-of-the-art pharmaceutical manufacturing projects that use new and innovative technologies to deliver a quality product while reducing the manufacturing cost. The winner will be selected and announced at the ISPE Annual Meeting in November 2007. See the details of the best pharmaceutical manufacturing facilities from around the world
- Tradeshow – an opportunity to see a wide range of equipment, products, and services and to source for new suppliers
- Student Poster Competition and Career Fair – an excellent opportunity for students to present their poster and win a grand prize of an opportunity to present their posters at the ISPE Annual Meeting 2007

For more information on the Conference Program visit http://www.ispesingaporeconference.com

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
March/April 2007, Vol. 27 No. 2

Architects, Engineers – Constructors

CH2M Hill, PO Box 22508, Denver, CO 80222, www.ch2mhill.com. See our ad in this issue.

CRB Consulting Engineers, 7410 N.W. Tiffany Springs Pkwy., Suite 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

IPS – Integrated Project Services, 2001 Joshua Rd., Lafayette Hill, PA 19444. (610) 828-4090. See our ad in this issue.

Parsons, 150 Federal St., Boston, MA 02110. (617)-946-9400. See our ad in this issue.

Stantec Consulting, 201 Old Country Rd., Suite 301, Melville, NY 11747. (631) 424-8600. See our ad in this issue.

Cleanroom Products/Services

AES Clean Technology, 422 Stump Rd., Montgomeryville, PA 18936. (215) 393-6810. See our ad in this issue.

Employment Opportunities

Fabricating Distributors Wanted for **AdvantaPure's** Sanitary Tubing, Hose, and Assemblies. Contact dschwass@advantapure.com for Available Territories.

Employment Search Firms

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

Filtration Products

Millipore Corp., 290 Concord Rd., Billerica, MA 01822. (800) MILLIPORE. See our ad in this issue.

Siemens Water Technologies, 125 Rattlesnake Hill Rd., Andover, MA 01810. (978) 470-1179. See our ad in this issue.

Hoses/Tubing

AdvantaPure, 145 James Way, Southampton, PA 18966. (215) 526-2151. See our ad in this issue.

Label Removal Equipment

Hurst Corp., Box 737, Devon, PA 19333. (610) 687-2404. See our ad in this issue.

Passivation and Contract Cleaning Services

Active Chemical Corp., 4520 Old Lincoln Hwy., Oakford, PA 19053. (215) 676-1111. See our ad in this issue.

Astro Pak Corp., 3187 Redhill Ave., Suite 105, Costa Mesa, CA 92626. (800) 743-5444. See our ad in this issue.

Passivation and Contract Cleaning Services (cont.)

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

Oakley Specialized Services, Inc., 50 Hampton St., Metuchen, NJ 08840. (732) 549-8757. See our ad in this issue.

Pumps

Watson-Marlow Bredel, 220 Ballardvale St., Wilmington, MA 01887. (978) 658-6168. See our ad in this issue.

Sterile Products Manufacturing

Tanks/Vessels

Lee Industries, PO Box 688 Philipsburg, PA 16866. (814) 342-0470. See our ad in this issue.

Used Machinery

Validation Services

ProPharma Group, 10975 Benson Dr., Suite 330, Overland Park, KS 66210; 5235 Westview Dr., Suite 100, Frederick, MD 21703. (888) 242-0559. See our ad in this issue.

Water Treatment

Christ Pharma & Life Science AG, Haupstrasse 192, 4147 Aesch, Switzerland. +41 617558111. See our ad in this issue.