

The Product Quality Research Institute (PQRI) is collaborative effort between the pharmaceutical industry, regulatory agencies, and academia. One of the purposes of PQRI is to promote discussion on current topics of interest in the pharmaceutical field. To that end, PQRI commissioned a working group to develop a White Paper that discusses the concept of process robustness and how it applies to development, scale up, and manufacture of pharmaceutical products.

Process Robustness – A PQRI White Paper

by PQRI Workgroup Members

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Introduction

Objective

The ability of a manufacturing process to tolerate the expected variability of raw materials, operating conditions, process equipment, environmental conditions, and human factors is referred to as robustness.

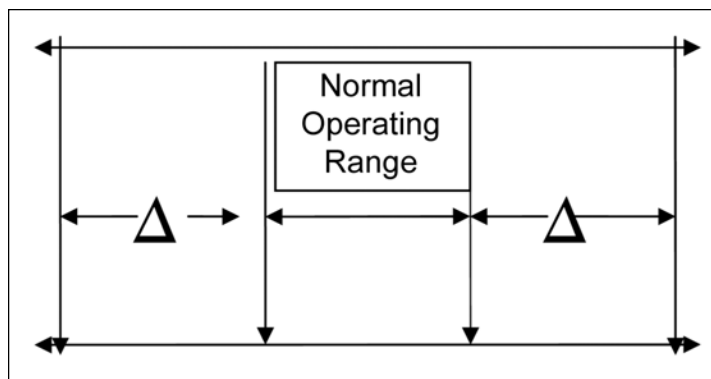
The objective of this paper is to unify understanding of the current concepts of process robustness and how they apply to pharmaceutical manufacturing. The paper also provides recommendations on development and maintenance of a robust process. The concepts presented here are general in nature and can apply to many manufacturing situations; however, the focus of the discussion is application of robustness principles to non-sterile solid dosage form manufacturing. The tools, case studies, and discussion presented in this paper center around new product development and commercialization as, ideally, process robustness activities start at the earliest stages of process design and continue throughout the life of the product. It is also recognized that concepts of robustness can be applied retrospectively to established products in order to enhance process understanding.

Background

There is a heightened emphasis on greater process understanding in the pharmaceutical industry. There is great incentive from a manufacturer's point of view to develop robust processes. Well understood, robust processes suggest greater process certainty in terms of yields, cycle times, and level of discards. Lower final product inventories may be carried if the manufacturing process is reliable.

There is a growing expectation from global regulatory agencies that firms demonstrate a comprehensive understanding of their processes and controls. The finalized FDA report entitled "Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach" clearly expresses the expectation that firms strive for "the implementation of robust manufacturing processes that reliably produce pharmaceuticals of high quality and that accommodate process change to support continuous process improvement." As evidenced by recent draft guidelines, the other members of the ICH tripartite have also adopted the philosophy embraced by this "Risk-Based Approach." The eventual implementation of recommendations contained in ICH Q8 and Q9 should establish the linkage between "knowledge" and "associated risk." An underlying principle of ICH Q8 is that an assessment of process robustness can be useful in risk assessment and risk reduction. Furthermore, such an assessment of process robustness can potentially be used to support future manufacturing and process optimization, especially in conjunction with the use of structured risk management tools outlined in the draft ICH Q9 guidance. The

Figure 1. Proven Acceptable Range (PAR).



establishment of robust processes serves the best interests of the patients, global regulatory agencies, and firms. It is anticipated that such processes will consistently produce safe and efficacious products in a cost effective manner. While not in the scope of this document, it is also anticipated that regulatory agencies will adjust their oversight requirements for processes that are demonstrated to be robust, as such processes are anticipated to present low risk for product quality and performance.

There is more to a robust process than having a dosage form pass final specifications. Robustness cannot be tested into a product; rather, it must be incorporated into the design and development of the product. Performance of the product and process must be monitored throughout scale up, introduction, and routine manufacturing to ensure robustness is maintained and to make adjustments to the process and associated controls if necessary. Process understanding - how process inputs affect key product attributes - is the key to developing and operating a robust process.

This paper presents key concepts associated with process robustness, defines common terms, details a methodical approach to robust process development, and discusses tools and metrics that can be used during development or for ongoing process monitoring. Where appropriate, case studies are used to demonstrate concepts. The tools, approaches, and techniques discussed are commonly understood concepts and are routinely used in other industries. Many pharmaceutical development and manufacturing programs are employing some or all of the techniques. The intent is to organize the approaches and show how, when used together, they can lead to greater process understanding and control.

Principles of Process Robustness

Defining Robustness

The ability of a process to demonstrate acceptable quality and performance while tolerating variability in inputs is referred to as robustness. Robustness is a function of both formulation and process design. Formulation design variables include the qualitative and quantitative composition of raw materials, both API and excipients. Process design variables include the process selected, the manufacturing sequence or steps, the equipment settings, such as speeds and feed rates, and environmental conditions. In this discussion, all process inputs will be referred to as parameters.

Performance and variability are factors impacting robustness and may be managed through process design and product composition. Elements of product composition for consideration include the choice of API form, since some API forms are more robust than others, and the choice of the excipients, e.g., the grades and concentrations.

Process performance and variability may be managed through the choice of manufacturing technology. Setting appropriate parameter ranges for a robust process requires consideration of the manufacturing technology selected. Special considerations are needed for situations/processes where the appropriate setting of one parameter depends on the setting of another. Well designed processes reduce the poten-

tial for human mistakes, thereby contributing to increased robustness.

A typical pharmaceutical manufacturing process is comprised of a series of unit operations. A unit operation is a discrete activity e.g., blending, granulation, milling, or compression. Parameters for a unit operation include: machinery, methods, people, material (API, excipients, material used for processing), measurement systems, and environmental conditions. The outputs of a unit operation are defined as attributes, e.g., particle size distribution or tablet hardness.

During product and process development both the inputs and outputs of the process are studied. The purpose of these studies is to determine the critical parameters and attributes for the process, the tolerances for those parameters, and how best to control them. Various experimental and analytical techniques may be used for process characterization. The goal of this development phase is to have a good understanding of the process and the relationships of the parameters to the attributes. The body of knowledge available for a specific product and process, including critical quality attributes and process parameters, process capability, manufacturing and process control technologies and the quality systems infrastructure is referred to as the Manufacturing Science underlying a product and process.

Critical Quality Attributes (CQAs)

There are some measured attributes that are deemed critical to ensure the quality requirements of either an intermediate or final product. The identified attributes are termed Critical Quality Attributes (CQAs).

CQAs are quantifiable properties of an intermediate or final product that are considered critical for establishing the intended purity, efficacy, and safety of the product. That is, the attribute must be within a predetermined range to ensure final product quality. There may be other non-quality specific attributes that may be identified, e.g., business related attributes, however, and they are outside the scope of CQAs.

Critical Process Parameter (CPPs)

During development, process characterization studies identify the Critical Process Parameters (CPPs). A Critical Process Parameter is a process input that, when varied beyond a limited range, has a direct and significant influence on a Critical Quality Attribute (CQA). Failure to stay within the defined range of the CPP leads to a high likelihood of failing to conform to a CQA.

It is also important to distinguish between parameters that affect critical quality attributes and parameters that affect efficiency, yield, or worker safety or other business objectives. Parameters influencing yield and worker safety are not typically considered CPPs unless they also impact product quality.

Most processes are required to report an overall yield from bulk to semi-finished or finished product. A low yield of a normally higher yielding process should receive additional scrutiny since the root cause for the low yield may be indica-

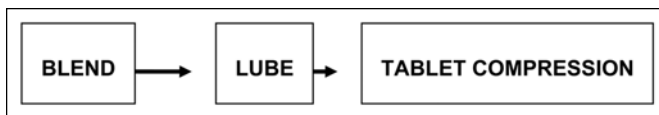


Figure 2. Case study example: process flow diagram for a direct compression tablet.

tive of a manufacturing issue or may be resultant from a lack of process control. In the event a process produces a lower than expected yield, it becomes relevant to demonstrate thorough process understanding and control why the low yield occurred.

Development of comprehensive manufacturing science for the product will produce the process understanding necessary to define the relationship between a CPP and CQA. Often the relationship is not directly linked within the same unit operation or even the next operation. It is also important to have an understanding of the impact of raw materials, manufacturing equipment control, and degree of automation or prescriptive procedure necessary to assure adequate control. The goal of a well characterized product development effort is to transfer a robust process which can be demonstrated, with a high level of assurance, to consistently produce product meeting pre-determined quality criteria when operated within the defined boundaries. A well characterized process and a thorough understanding of the relationships between parameters and attributes will also assist in determining the impact of input parameter excursions on product attributes. CPPs are intrinsic to the process, and their impact on quality attributes is mitigated by process controls or modifications to other parameters.

Normal Operating Range (NOR), Proven Acceptable Range (PAR)

During the early stages of process development, parameter target values and tolerance limits are based on good scientific rationale and experimental knowledge gained from the laboratory and pilot scale studies. A parameter that shows a strong relationship to a critical quality attribute becomes a key focal point for further study. In developing the manufacturing science, a body of experimental data is obtained, and the initially selected parameter tolerances are confirmed or adjusted to reflect the data. This becomes the Proven Acceptable Range (PAR) for the parameter, and within the PAR an operating range is set based on the typical or Normal Operating Range (NOR) for the given parameter. Tolerance ranges may be rationalized and adjusted as increased process understanding is gained.

Further study of parameters is a prelude to determining those that are critical process parameters. If varying a parameter beyond a limited range has a detrimental effect on a critical quality attribute, it is defined as a Critical Process Parameter (CPP). Final selection and characterization of the critical process parameters should be completed prior to executing the commercial scale batches.

In subsequent product development the parameters and attributes of the process are characterized to determine the critical parameters for the process, the limits for those pa-

rameters, and how best to control them. Controllable parameters may be parameters that are adjustable, e.g., drying time or temperature. At other times it may be desirable to ‘fix’ a parameter by specifically setting one value and not testing around the variability. A cause and effect relationship may be established for parameters and desired attributes. As an example, the drying time and temperature are parameters to a granulation process that affect the moisture level, an attribute of the granulation.

In a robust process, critical process parameters have been identified and characterized so the process can be controlled within defined limits for those CPPs. The NOR of the process is positioned within the PAR for each of the CPPs. The PAR is a function of the process and reflects the range over which a parameter can vary without impacting critical quality attributes. A process that operates consistently in a narrow NOR demonstrates low process variability and good process control. The ability to operate in the NOR is a function of the process equipment, defined process controls and process capability. If the difference, delta, between the NOR and PAR is relatively large, the process is considered robust with respect to that parameter. Refer to Figure 1. Where the delta between the NOR and PAR is relatively small, adequate process control and justification should be provided to assure the process consistently operates within the PAR.

Characterizing and defining parameters may take a path of first defining the NOR and range midpoint where the commercial product would be expected to be consistently manufactured, followed by defining the boundaries of the PAR. A process that operates in a NOR that is close in limits to the PAR may experience excursions beyond the PAR. In this case, the process may lack robustness

In processes that contain CPPs, and where the between the NOR and PAR is relatively small, the concern of excursions beyond the PAR drives the need for a greater understanding of the tolerances of the CPPs. This is warranted to assure adequate process control is provided within the process.

Further characterization of parameters is achieved as manufacturing experience is gained and the state of robustness of the process is assessed.

Variability: Sources and Control

Typical sources of variability may include process equipment capabilities and calibration limits, testing method variability, raw materials (e.g. API and excipient variability between lots and vendors), human factors for non-automated pro-

Critical Quality Attributes
Dissolution Assay Tablet uniformity Blend uniformity Stability

Table A. Case study example: Table of Critical Quality Attributes (CQAs) for a direct compression tablet. (Note that this list is for the case study example only and may not be all inclusive).

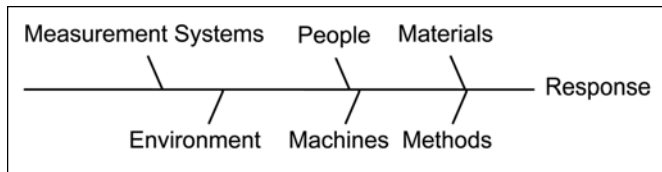


Figure 3. General concept for Fishbone (Ishikawa) diagram.

cesses, sampling variability, and environmental factors within the plant facility. A myriad of systems are available to monitor and control many of the input factors listed.

Variability in operator technique may contribute to process variability. In assessing robustness of a process it may be necessary to evaluate operator-to-operator variability and day-to-day variability of the same operators. Ideally, processes are designed to minimize the effect of operator variability.

Setting Tolerance Limits

Upper and lower tolerances around a midpoint within the PAR of a parameter should be established to provide acceptable attributes. In setting the acceptable tolerances of a CPP often the point of failure does not get defined. It is acknowledged that the acceptance limits set for a CPP may be self-limited by the initially selected design space. In this case, the manufacturing science knowledge base may be limited; however, within the tolerance limits selected, conformance to the desired quality attribute limits will be achieved and the manufacturing science knowledge is sufficient.

It is not necessary to take a process to the edge of failure to determine the upper and lower limits of a defined process. The defined limits, however, should be practical and selected to accommodate the expected variability of parameters, while conforming to the quality attribute acceptance criteria.

Development of a Robust Process

A systematic team-based approach to development is one way to gain process understanding and to ensure that a robust

process is developed. However, there is presently no guidance on how to develop a robust process. The purpose of this section is to define a systematic approach to developing a robust process and to determine which parameters are CPPs. This section will also present a case study to give practical examples of tools that can be used in the development of a robust process.

It is important to realize that this is only one way that process robustness can be achieved. There are other methods that are equally valid for development of a robust process. Note that this process can be applied interactively throughout the product lifecycle.

Steps for Developing a Robust Process

Six steps are described for the development of a robust process:

1. Form the team.
2. Define the process (process flow diagram, parameters, attributes).
3. Prioritize experiments.
4. Analyze measurement capability.
5. Identify functional relationships.
6. Confirm critical quality attributes and critical process parameters.

It is important to note that documentation of results is a critical part of this process, and appropriate records should capture all findings of the development process.

Step 1: Form the Team

Development of a robust process should involve a team of technical experts from R&D, technology transfer, manufacturing, statistical sciences, and other appropriate disciplines. The scientists and engineers most knowledgeable about the product, the production process, the analytical methodology, and the statistical tools should form and/or lead the team.

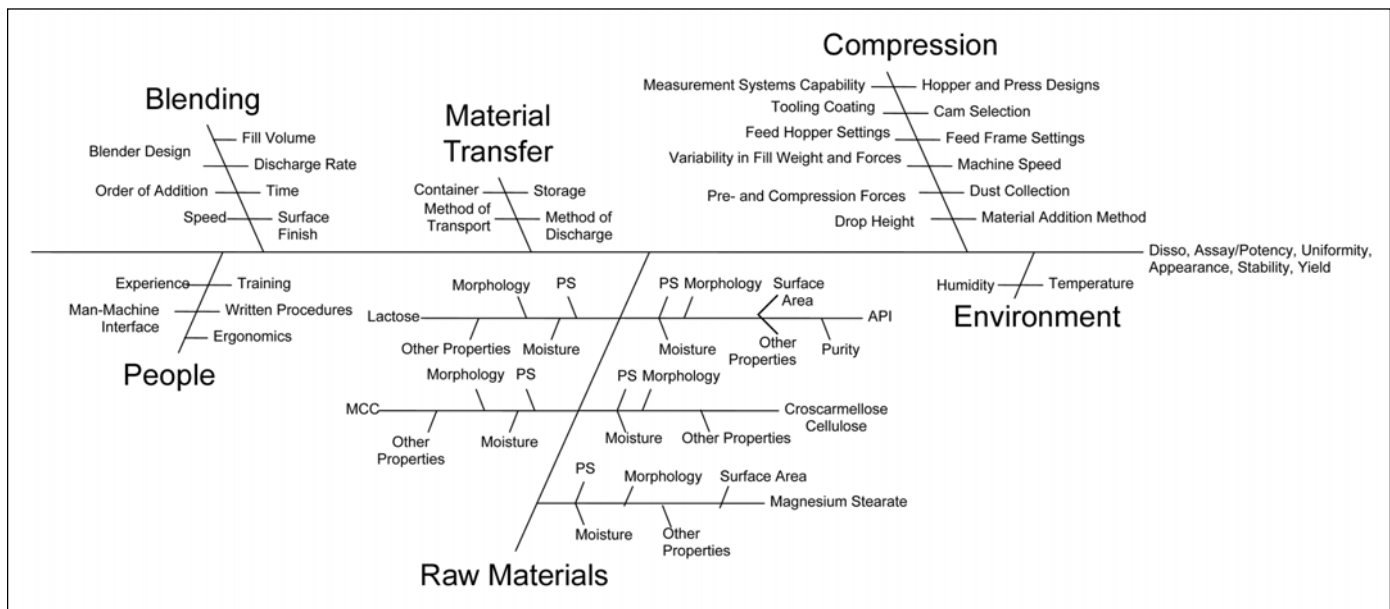


Figure 4. Case study example: Fishbone diagram for a direct compression tablet.

This team approach to jointly develop the dosage form eliminates the virtual walls between functions, improves collaboration, and allows for early alignment around technical decisions leading to a more robust product. This team should be formed as early as possible, before optimization and scale-up has been initiated.

Step 2: Define the Process

A typical process consists of a series of unit operations. Before the team can proceed with development of a robust process they must agree on the unit operations they are studying and define the process parameters and attributes. Typically, flow charts or process flow diagrams are used to define the process. This flowchart should have sufficient detail to readily under-

stand the primary function of each step. Figure 2 illustrates a simple process flow diagram for the case study of a direct compression tablet.

The next step in defining the process is to list all possible product attributes and agree on *potential* Critical Quality Attributes (CQAs). This list of product attributes is typically generated by the team using expert knowledge, scientific judgment, and historical information on the product of interest and similar products. It should be emphasized that some attributes are evaluated or monitored for process reproducibility, i.e., process yield, and some are for final product quality, i.e., the critical quality attributes. For example, critical quality attributes could include (but are not limited to) assay, dissolution, degradants, uniformity, lack of micro-

Appendix A Potential Critical Process Parameters for Common Solid Dosage Form Unit Operations

Blending

- Blend Time
- Rotation Rate
- Agitator Speed
- Room Temperature, Humidity

Dry Granulation (Roller Compaction)

- Roll Speed
- Feed Screw Speeds
- Roll Force/Pressure
- Roll Separation/Gap
- Room Temperature, Humidity

Milling

- Impeller Speed
- Feed Rate
- Room Temperature, Humidity

Fluid Bed Granulation

- Granulation Fluid Mixing Time
- Granulation Fluid Mixing Speed
- Granulating Fluid Amount
- Granulating Fluid Addition Rate
- Granulating Fluid Temperature
- Spray Nozzle Air Volume
- Bed Mixing Time
- Supply Air Flow Rate, Temperature, Dew Point
- Product Bed Temperature
- Exhaust Air Temperature, Dew Point
- Filter Shaking Intervals

Wet Granulation

- Granulation Fluid Mixing Time
- Granulation Fluid Mixing Speed
- Granulating Fluid Amount
- Granulating Fluid Addition Rate
- Granulating Fluid Temperature
- Spray Nozzle Air Volume

- Dry Mixing Time
- Wet Mixing Time
- Impeller Speed
- Chopper Speed
- Power Consumption

Cabinet Drying

- Supply Air Temperature, Dew Point
- Drying Time
- Final Moisture Content

Fluid Bed Drying

- Supply Air Flow Rate, Temperature, Dew Point
- Product Bed Temperature
- Exhaust Air Temperature, Dew Point
- Filter Shaking Intervals
- Final Moisture Content

Compression

- Tablet Weight
- Turret Speed
- Main Compression Force
- Pre-Compression Force
- Feeder Speed
- Upper Punch Entry
- Room Temperature, Humidity

Film Coating

- Coating Suspension Mixing Time
- Coating Suspension Mixing Speed
- Coating Suspension Amount
- Coating Suspension Spray Rate
- Atomization Pressure
- Pan Rotation Speed
- Preheat Time
- Supply Air Flow Rate, Temperature, Dew Point
- Product Bed Temperature
- Exhaust Air Temperature, Dew Point

bial growth, and appearance. For the case study of a direct compression tablet, Table A lists the potential critical quality attributes that the team generated.

The final step in defining the process is determining process parameters. Categories of parameters to consider are materials, methods, machine, people, measurement, and environment. In some cases, the parameters may be some or all of the actual attributes of a previous unit operation. Several methods or tools can be used to capture the parameters. One suggested tool is called a Fishbone or Ishikawa diagram. The general concept is illustrated in Figure 3. Refer to Appendix A for a listing of common unit operations and possible critical process parameters for solid dosage form manufacturing. A fishbone diagram for the case study of a direct compression tablet process is shown in Figure 4.

Step 3: Prioritize Experiments

A thorough understanding of the process and the process parameters is needed to develop a robust process. However, it is not practical or necessary to study every possible relationship between process parameters and attributes. It is recommended that the team initially use a structured analysis method such as a prioritization matrix to identify and prioritize both process parameters and attributes for further study. Unlike more statistically-oriented techniques, the use of a prioritization matrix generally relies on the process knowledge and technical expertise of the team members involved in the process under study, although data may be included from designed experiments.

A case study example of a prioritization matrix for a direct compression tablet is shown in Table B. In the table is placed a quantitative measure of the effect that a particular parameter is expected to have on a measured product characteristic. This effect is typically expressed on a scale from 0 (no influence) to 10 (directly correlated). A ranking of parameters of importance is calculated by considering the expected impact of a parameter on attributes as well as the relative importance of the attributes. In this case study, three process parameters, API particle size, compression force, and compressing speed are anticipated to be the most important

(based on the ranking totals at the bottom of the table). Therefore, for this case study, it makes sense to prioritize studies that focus on the effects of these three parameters. The parameters that were of lower importance may not be studied at all, or may be studied at a later date.

Step 4: Analyze Measurement Capability

All measurements are subject to variability. Therefore, the analysis of a process cannot be meaningful unless the measuring instrument used to collect data is both repeatable and reproducible. A Gage Repeatability and Reproducibility study (R&R) or similar analysis should be performed to assess the capability of the measurement system for both parameters and attributes. Measurement tools and techniques should be of the appropriate precision over the range of interest for each parameter and attribute.

Step 5: Identify Functional Relationship Between Parameters and Attributes

The next step is to identify the functional relationships between parameters and attributes, and to gather information on potential sources of variability. The functional relationships can be identified through many different ways, including computational approaches, simulations (small scale unit ops) or experimental approaches. Where experimental approaches are needed, one-factor-at-a-time experiments can be used, but are least preferred. Design Of Experiments (DOE) is the recommended approach because of the ability to find and quantitate interaction effects of different parameters

Properly designed experiments can help maximize scientific insights while minimizing resources because of the following:

- The time spent planning experiments in advance can reduce the need for additional experiments.
- Fewer studies are required.
- Each study is more comprehensive.
- Multiple factors are varied simultaneously.

PROCESS PARAMETERS									
Quality Attributes	Blend Time	Lube Time	API Particle Size	Pre-Compression Force	Compression Force	Compressing Speed	Feed Frame Setting	Excipient Particle Size	Importance
Dissolution	1	7	9	1	9	1	3	1	10
Assay/ Potency	1					5	3		10
Uniformity	7	1	9			5	3	5	10
Appearance	1	3			3	3			5
Stability			1		3				7
Yield						3			3
Ranking Total	95	95	187	10	126	134	90	60	
Percent	13	13	25	1	17	18	12	8	

Table B. Case study example: Prioritization matrix for a direct compression tablet (Note that this matrix is for the case study example only and may not be all inclusive).

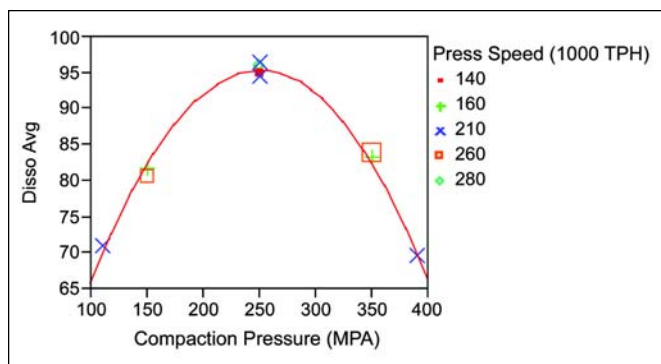


Figure 5. Case study example: DOE results showing effect of compaction pressure on dissolution.

Design of experiments can often be a two-stage process, involving screening experiments to identify main factors to consider as well as response surface methodologies to refine the understanding of functional relationships between key parameters and attributes. An example of a statistical DOE for the case study of a direct compression tablet is shown in Table C.

Step 6: Confirm Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs)

After a sufficient amount of process understanding is gained, it is possible to confirm the CQAs previously identified (step 2). In the case study for a direct compression tablet, the critical quality attributes were dissolution, assay, tablet uniformity, and stability. As defined in a previous section, a CPP is defined as a process input that has a direct and significant influence on a CQA. CPPs are typically identified using the functional relationships from step 5. In the case study for a direct compression tablet, tablet press speed and compression pressure were found to impact the CQA of dissolution, and were identified as CPPs. In Figure 5, it can be seen that there is an optimum compaction pressure to obtain the highest dissolution. In Figure 6, it can be seen that increasing the tablet press speed resulted in increasing variability in dissolution.

These functional relationships can be used and various optimizing strategies employed to identify optimal process set points or operating regions for press speed and compaction pressure. Suppose the product's goal is to achieve an average dissolution greater than 80% with less than a 5% standard deviation on dissolution. One summary source providing information on a potential operating region is an overlay plot; see Figure 7 for the case study of a direct compression tablet. This visual presents a predicted (yellow) area of goodness where average dissolution is greater than 80% and simultaneously the standard deviation of dissolution is less than 5%. The area where either or both of these conditions fails to hold is colored grey; the actual experimental design points are shown as red dots on the plot.

Technology Transfer

Process understanding is necessary for development of a robust process. The systematic, step-wise approach described above may require several iterations before enough process

understanding is achieved. This methodology will enable scientists and engineers to gain process understanding to set the groundwork for a robust operation in production. Important to the product technology transfer is a well-characterized formulation and process design. It is recognized that parameters identified during the research and development phase may need to be adjusted at scale-up to the pivotal (biobatch) or commercial batch size. Therefore, employing similar steps that are used in the development of a robust process, scale-up activities will include the challenging of previously defined CPPs and CQAs and identification and process optimization of newly identified process parameters. These activities will require an understanding of:

- the qualitative and quantitative composition of the product
- API, excipient specifications and functional attributes
- potential increased variability in the API as a result of scale-up of the API manufacturing process
- manufacturing process and controls, operator experience, and skill sets
- Assessment of equipment, used at the development stage versus the identified commercial manufacturing equipment, to identify batch sizes and operating parameters. This equipment assessment should also include equipment controls and tolerances.

After CQAs and CPPs have been defined, the team should generate a plan for controlling CPPs. This may involve, but is not limited to establishment of process operating limits, use of automation, procedural controls and specialized operator training and qualification. In addition, it is critical that the knowledge transfer is well documented for the development and technology transfer phases through to the commercial scale.

Run Order	Compression Pressure (megaPascals)	Press Speed (1000 tab/h)	Dissolution (Average % dissolved at 30 min)	Disso SD
1	350	160	83.12	2.14
2	150	160	81.54	2.40
3	250	280	96.05	3.73
4	150	260	80.38	6.18
5	390	210	69.32	6.08
6	250	140	94.81	1.14
7	250	210	96.27	3.59
8	250	210	94.27	6.37
9	110	210	70.76	4.03
10	350	260	83.71	7.10

Table C. Case study example: DOE results for a direct compression tablet study. In this example, the effect of compression pressure and press speed on dissolution were studied. The results, plotted in Figures 5 and 6 showed that compression pressure affected average dissolution, while tablet press speed affected dissolution variability.

Process Robustness The ability of a manufacturing process to tolerate the variability of raw materials, process equipment, operating conditions, environmental conditions and human factors is referred to as robustness. Robustness is an attribute of both process and product design.			
R&D	Scale-Up and TT	Commercialization	Post-Commercialization
Establish basis for formulation, process, and product design.	Generate detailed characterization of process and product being transferred.	Maintain ideal process state and assess process robustness.	After a sufficient time of manufacture, the commercial scale assessment of robustness can be ascertained.
Understand relationship between critical process parameters (CPP) and critical to quality product attributes (CQA).	Establish the ability to manufacture product routinely and predictably to the desired quality and cost, in compliance with appropriate regulations.	Monitor and where necessary, actively control process.	Understand process capability and modify process if necessary to improve robustness.
Determine a design space that integrates various unit operations to achieve an output in the most robust, efficient and cost effective manner.	Confirm relationship between CPP and CQA.		Confirm relationship between CPP and CQA.
Tools: Flowcharts, Ishikawa Diagram, FMEA, QFD, KT, Gage R&R, DOE, Regression Analysis and Other Statistical Methods, PAT	Tools: Flowcharts, Ishikawa Diagram, FMEA, QFD, KT, Gage R&R, DOE, Regression Analysis and Other Statistical Methods, OC Curves, Tolerance and Confidence Intervals, PAT, Tolerance Analysis	Tools: SPC, Trend Plots/Run Charts, Gage R&R, Process Capability – Cpk, PAT	Tools: APR, SPC, Trend Plots/Run Charts, FMEA, QFD, KT, Ishikawa Diagram, Flow Charts, Pareto, DOE, Regression Analysis and Other Statistical Methods, PAT

Table D. Development of robustness at various stages in the Product Life Cycle.

As presented in the manufacturing section, with more manufacturing history and data over time, assessment of robustness can be ascertained.

Process Robustness in Manufacturing

The Research and Development (R&D) phase is characterized by execution of a development plan consisting of a number of discrete experiments that are designed to develop a formulation, establish the proper manufacturing process, and provide process and formulation understanding around the key relationships between parameters and attributes. When the product is transitioned to Manufacturing, it will most likely encounter a much wider range of variation on the parameters than seen in development. For example, attribute variability may increase due to a wider range in incoming raw material parameters that cannot feasibly be studied in R&D. It is upon transfer to Manufacturing that assessment of the true process capability and robustness as well as any process improvement or remediation will begin.

Manufacturing yields a large amount of empirical process performance data that may be used for a variety of purposes. It should be periodically analyzed to assess process capability and robustness and to prioritize improvement efforts; the data should be reviewed during the improvement effort to identify correlative relationships. Feedback to R&D may occur during these activities to further build quality into the design process. Although Manufacturing may benefit from a larger amount of empirical data, the ability to perform planned experimentation is not trivial. There are other techniques that have been successfully utilized to further process understanding and variability reduction. This section discusses techniques that are applicable to analyzing data to determine the state of process robustness and ensure the continuation of this state over time.

Monitoring the State of Robustness

As R&D has established the desired operating range of parameters and attributes, Manufacturing should monitor both the parameters and attributes over time and review the information at a pre-determined frequency, with emphasis on critical or key parameters.

The state of robustness may be monitored through using Statistical Process Control (SPC) charts combined with capability index calculations. SPC tools such as control charts can be used to ascertain the process' stability, provide warnings of any potential problems, and to assess the state of control. Capability indices assess the product or process ability to meet specifications. To evaluate the true state of robustness, information on process parameters and attributes should be collected as per a pre-determined SPC sampling plan. Process control charts (trend chart, run chart) are constructed and capability indices calculated.

- **Run Chart/Trend Chart:** A run chart or trend chart is an x-y plot that displays the data values (y) against the order in which they occurred (x). These plots are used to help visualize trends and shifts in a process or a change in variation over time.
- **Control Charts:** Similar to a run chart, a control chart is a plot of a process parameter or quality attribute over time. Overlaid on the plot is information about the process average and expected variability (control limits). Statistical probabilities form the basis for control chart rules that help identify odd process behavior. Identifying and removing assignable causes of variability to the extent that only smaller or common sources of variability remain produces a process that can be considered stable and predictable over time, or under statistical control and producing consistent output.

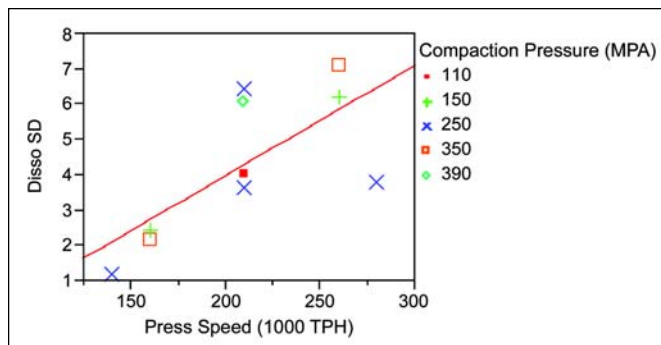


Figure 6. Case study example: DOE results showing effect of press speed on dissolution variability. (% standard deviation).

- **Process Capability:** After it has been determined that a process is in statistical control, i.e., all assignable sources of variability have been removed; the expected process capability can be calculated. The capability number provides an assessment as to what extent the process is capable of meeting specifications or other requirements. Common capability indices include:

- **C_p:** This index relates the allowable process spread (the upper specification limit minus the lower specification limit) to the total estimated process spread, $\pm 3s$. Generally, C_p should be as large as possible.
- **C_{pk}:** This index relates the relationships of centeredness and spread of the process to the specification limits. If the C_{pk} value is significantly greater than 1, the process is judged capable of meeting specifications. Larger values of C_{pk} are better.

Much has been written about control charts and process capability indices; there are formulas and statistical methods available for a wide range of data types, distributions, and specifications beyond the most common charts and indices for normally distributed, centered data with symmetric specifications. It should be noted that the distribution of the data under study must be matched to the appropriate control chart and capability index; data normality should not be assumed in all cases.

Data can be captured and processed in a variety of different ways. Electronic manufacturing process databases can facilitate monitoring the state of process robustness.

Process Specific Improvement or Remediation

It is Manufacturing's responsibility to work with the process within bounds defined by development and registration to attain and maintain a process in an ideal state. If a problem has been identified either by a trend within the operating range or a single point outside the operating range then an investigation should occur. Tools for investigation include:

- **Flowcharts:** A pictorial (graphical) representation of the process flow that shows the process inputs, activities, and outputs in the order in which they occur. Flowcharts aid process understanding.

- **Ishikawa or Cause and Effect (Fishbone) Diagram:** This tool helps organize and display the interrelationships of causes and effects. It is a form of tree diagram on its side and has the appearance of a fishbone.
- **QFD:** Quality Function Deployment is a structured analysis method generally used to translate customer requirements into appropriate technical requirements. It is used to capture and share process knowledge and may be used to identify and prioritize both process parameters (inputs) and characteristics (outputs).
- **FMEA:** Failure Modes and Effects Analysis provides a structured approach to identify, estimate, prioritize, and evaluate risk with the intention to prevent failures. Historically this tool is used in the design of a new product, process, or procedure; it can also be used to limit the risk involved in changing a process.
- **KT:** Kepner-Tregoe has developed four rational processes (situational, problem, decision, and opportunity) that provide systematic procedures for applying critical thinking to information, data, and experience; application of this tool aids the team's understanding and decision making.
- **Pareto Chart:** A graphical means of summarizing and displaying data where the frequency of occurrence is plotted against the category being counted or measured. It is used to pictorially separate the significant few causes from the many and identify those areas that are of the most concern and should be addressed first.

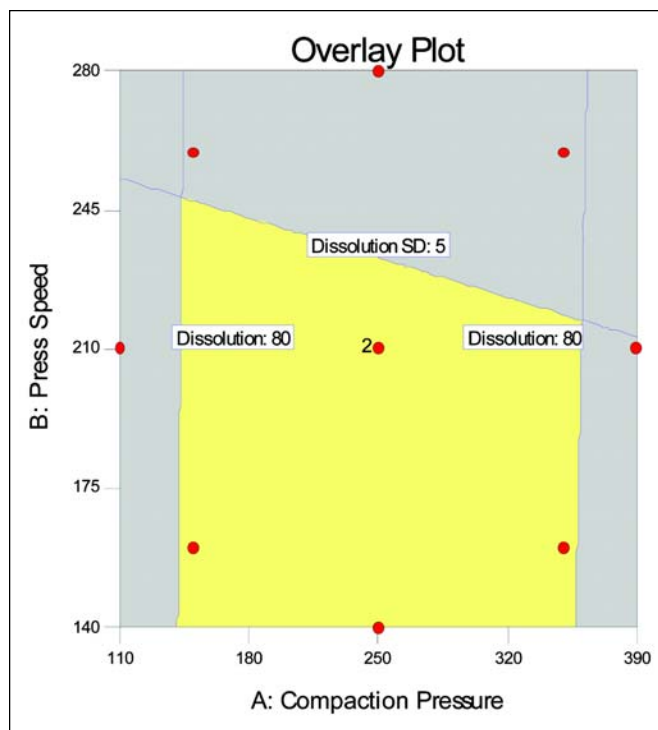


Figure 7. Case study example: Overlay plot of DOE results showing effect of compaction pressure and press speed on dissolution. The potential operating window is shown in yellow.

If either the variability of the process is larger than expected or the process average is not as expected, historical data analysis may be used to help provide root cause candidates. Process improvement or remediation activities may need to occur using Statistical Experimental Design.

- **DOE (Design of Experiments):** Uses a statistically based pattern of experimental runs to study process parameters and determine their effect on process attributes. The results of these experiments are used to improve or optimize the process and may be used to predict the process's ability to produce the product within the specifications.
- **Regression/correlation analysis/ANOVA:** These are mathematical approaches to examine the strength of the relationship between two or more variables. These methods and models are useful in determining root cause, in specification setting, and optimization. When applied to historical data analysis, care should be taken in concluding causal relationships.
- **r/t-tests/F-tests:** Statistically significant relationships are determined using these statistics; in regression the t-test is used, correlation analysis employs r, and ANOVA relies on the F-test.
- **Scatter Diagrams:** A visual display of data showing the association between two variables. The scatter diagram illustrates the strength of the correlation between the variables through the slope of a line. This correlation can point to, but does not prove, a causal relationship.

Plant-wide Variability Reduction Activities

In addition to the targeted improvement or remediation activities just discussed, process variability may be reduced through plant-wide process improvement initiatives aimed at general sources of variability. Recent industry initiatives and programs targeted at variability and cost reductions and efficiency and flow improvements include 6-sigma, lean manufacturing, and even lean sigma.

General sources of process variability include machines, methods, people, materials, measurement systems, and environment. Examples of variability reduction/process improvement activities that address the general sources of variability and will lead to improved processes include: instrumentation calibration and maintenance, gage R&R studies, operator skills assessment, general plant layout, and clearly written work instructions.

- **Materials** can be a significant source of process variability. It is important that the material functionality and specific physiochemical specifications are well understood. If some aspect of the material is critical, then it should be controlled.

- **Instrumentation and Machine Calibration and Maintenance:** Machine and measurement systems are two of the process components whose variability can contribute adversely to the product. Planned maintenance, repeatability, reproducibility, and accuracy checks should be performed as per a systematic schedule. The schedule frequency should be appropriate for maintaining calibration. In addition, it is critical that the preventative maintenance program addresses equipment parameters that are process critical, i.e., granulator impeller speeds, air flow in fluid-bed equipment, and film coaters.
- **Gage R&R Studies:** It is difficult/impossible to place a response in control if the measurement system is not capable. The gage or measurement system R&R experimental design study provides information about the repeatability (inherent equipment variation) and reproducibility (operator to operator variation) of the measurement system's actual vs. required performance. More generally, a measurement system analysis can be used to study bias, linearity, and stability of a system.
- **Human Factors:** This contribution to variability is best minimized through education and training. The operator skills assessment provides a tool to track required skills vs. personnel capability. Variability in how a task is performed can be reduced if the work instructions are clear and concise. These instructions along with the general process flow should be periodically reviewed and discussed. Systematically error proofing is also a way to reduce the influence of the human factor.
- **Plant Layout:** Along with other environmental factors of temperature, pressure, and humidity, etc., the general cleanliness, orderliness, and layout of an area provides an indirect effect on the variation of a product. Environmental plans should be developed and maintained.

Conclusion

Creating a system that facilitates increased process understanding and leads to process robustness benefits the manufacturer through quality improvements and cost reduction. Table D summarizes the robustness roles by product life cycle along with useful tools for each stage. This system for robustness begins in R&D at the design phase of the formulation and manufacturing processes; emphasis on building quality into the product at this stage is the most cost effective strategy. R&D quantifies relationships between the inputs and outputs; the processes are established to produce the best predicted output with the targeted amount of variability.

Information about the process settings and key relationships are communicated to Manufacturing. Upon transfer, Manufacturing begins to verify R&D's information on process robustness through process monitoring and data analysis. Both general and process specific improvement activities help Manufacturing attain and maintain its goals.

Glossary

Critical Process Parameter (CPP) - A Critical Process Parameter is a process input that, when varied beyond a limited range, has a direct and significant influence on a Critical Quality Attribute.

Critical Quality Attribute (CQA) - A quantifiable property of an intermediate or final product that is considered critical for establishing the intended purity, efficacy, and safety of the product. That is, the property must be within a predetermined range to ensure final product quality.

Design Space - The design space is the established range of process parameters that has been demonstrated to provide assurance of quality. In some cases design space can also be applicable to formulation attributes.

Manufacturing Science - The body of knowledge available for a specific product and process, including critical-to-quality product attributes and process parameters, process capability, manufacturing and process control technologies, and the quality systems infrastructure.

Normal Operating Range (NOR) - A defined range, within the Proven Acceptable Range (PAR), specified in the manufacturing instructions as the target and range at which a process parameter should be controlled, while producing unit operation material or final product meeting release criteria and CQAs.

Process Analytical Technologies (PAT) - 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 assuring final product quality.

Proven Acceptable Range (PAR) - A characterized range at which a process parameter may be operated within, while producing unit operation material or final product meeting release criteria and CQAs.

Quality - Degree to which a set of inherent properties of a product, system or process fulfills requirements.

Quality System - Formalized system that documents the structure, responsibilities, and procedures required to achieve effective quality management.

Requirements - Needs or expectations that are stated, generally implied, or obligatory by the patients or their surrogates (e.g., health care professionals, regulators, and legislators).

Repeatability - The variability obtained with one gage used several times by one operator.

Reproducibility - The variability due to different operators using the same gage on the same part.

Robustness - The ability of a product/process to demonstrate acceptable quality and performance while tolerating variability in inputs.

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Who has not heard about avian flu? A threat of pandemic influenza came on the world's radar screen with the emergence of the H5N1 influenza strain. In this article, we will talk about what we have learned from previous pandemics; how to mitigate fear and uncertainty; and some key parts of a strategic business management plan for pandemics.

Avian Flu – Is My Company Prepared?

by Wendy Haines and Martin Rock

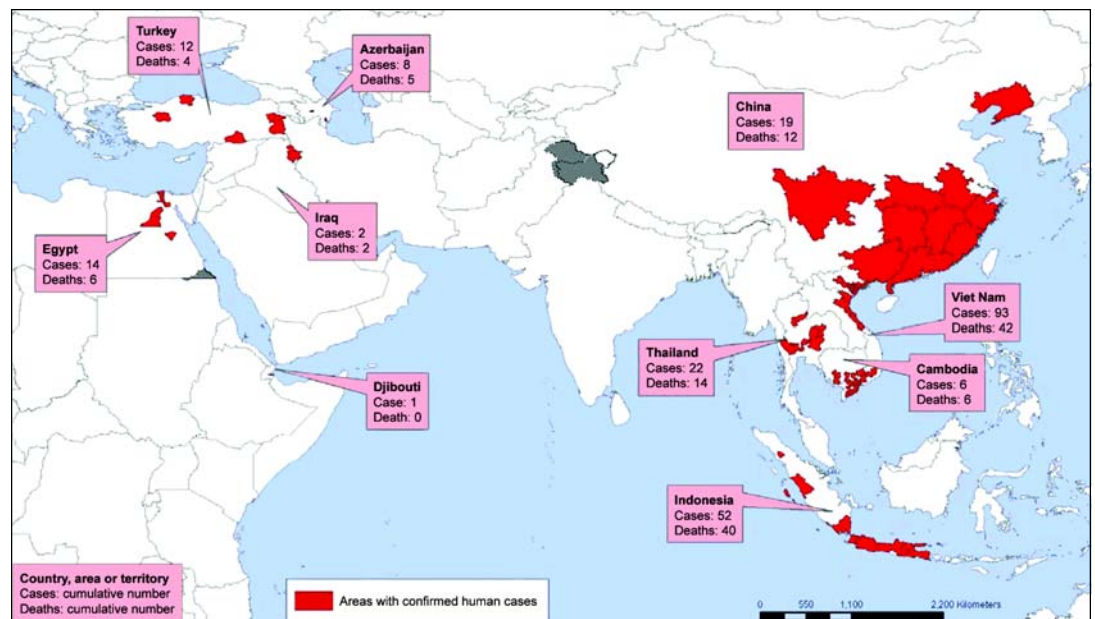
Who has not heard about avian flu? Avian flu articles have appeared in recent HR magazines, the Harvard Business Review, CFO Journal, numerous news briefs have been posted on the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) Websites, plus this issue also has appeared on the national news. The Kubu Simbelang village of North Sumatra, Indonesia got the world's attention through mainstream media when a single extended family contracted the H5N1 strain of avian influenza and this resulted in seven fatalities. According to the Ministry of Health in Indonesia, there have been 54 confirmed cases of H5N1 avian influenza and 42 have been fatal (as of July 20, 2006).¹ The H5N1 cases in Indonesia have gotten people speculating – is this the launch of a global pandemic influenza?

What Have we Learned?

George Santayana once said, “Those who do not learn from history are doomed to repeat it.”² What has been learned from the pandemic

influenzas in this century? First, the most devastating flu pandemic, the “Spanish Flu” (H1N1) killed more than 500,000 people in the United States with estimates between 20 to 50 million people worldwide.³ According to epidemiologists, one of the most interesting findings, from the Spanish Flu was the shape of the mortality curve.⁴ The mortality curve was a “W” shape, with three peak age groups for mortality, which means that the sensitive populations were the very young, adolescents, and the elderly. Normally, the mortality curve is a “U” shape. This shape means that the mortality rate was highest for both the young and the old. Literature searches have revealed that epidemiologist do not have an answer to explain the “W” shaped mortality curve of the 1918 Flu. However, some suggest that there was a possible pre-cursor wave of flu that occurred 30 years prior to the 1918 Flu. The pre-cursor flu could have given a level of immunity to the elderly, but this immunity would not have been seen in young adults who were not born during this time.⁵ Similar to the 1918 Flu, the sensitive populations for H5N1 avian influenza has been the very young

Figure 1. Affected areas with confirmed human cases of H5N1 avian influenza since 2003. (Source: WHO, 7 July 2006).



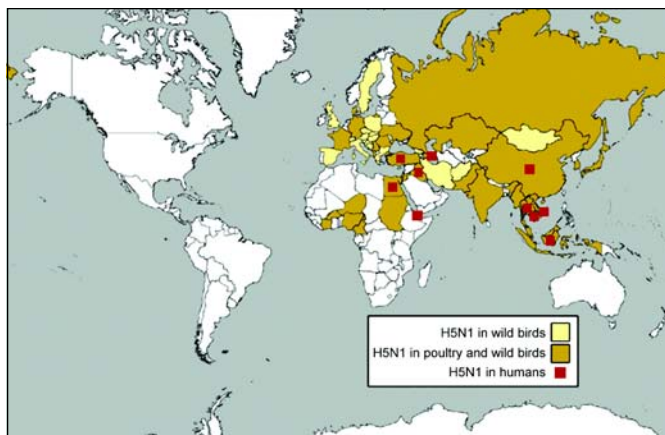


Figure 2. Pandemic Planning Update II. (Source: Dept. of Health and Human Services, 29 June 2006).

and adolescents.

Second, there are more improved ways of disseminating information regarding a pandemic threat, but the rate in which a pandemic influenza can spread is increased due to a more global society. Consider this possible scenario. Five people from different countries board an airplane going to the same three-day conference. Two days later, Person A has a sore throat, but thinks nothing of it and continues attending the conference. Another two days go by, Person A now has a fever, sore throat, and muscle aches. Persons B and C both also have a sore throat, while persons D and E have a sore throat, fever, chills, and muscle aches. All of these people board airplanes to return home to recuperate. What has just happened? Influenza has just been spread to five different countries around the world by a single airplane flight.

Third, a lot can be learned from countries that have successfully eliminated H5N1 from poultry. Hong Kong suffered multiple outbreaks of H5N1 in 2003, but remarkably, they were H5N1 free in 2004. How did Hong Kong accomplish this task? Hong Kong vaccinated every chicken against H5N1 and routinely tested chickens, pet birds, and wild birds. They closed live-poultry stalls so that they could be disinfected twice a month and inspected markets and farms continuously.⁶ Thailand also has spent a lot of time and effort to get H5N1 under control. Similar to Hong Kong, Thailand tests ducks for H5N1 in order to help ensure only virus-free ducks roam free and they have gotten the support of villagers to report any chicken die-offs. Thailand also has been able to handsomely reimburse farmers whose birds have been slaughtered.⁶

Therefore, sensitive population for H5N1 has been recognized, means can be identified to reduce the spread of influenza by globalization, and strategies can be learned from countries with previous outbreaks of H5N1. The question is whether this information will be used effectively.

Hidden Threats

Thinking back to the airplane scenario, we have already illuminated one hidden threat – the delay between infection and the signs and symptoms of the flu. Flu symptoms normally appear two days following initial exposure; however,

people are most infectious 24 hours prior to symptoms.⁴ Similar to the airplane scenario described above, an employee can come to work one day, interact with their colleagues and co-workers, and show no signs or symptoms of the flu. The same individual may be out sick the next day and would have spread the flu to the people he or she had interacted with during the previous 48 hours. Therefore, businesses will need to be pro-active with educating their employees about personnel hygiene, keeping track of exposures to sick people, and then advising employees to work from home. Companies can obtain information from the Centers for Disease Control and Prevention (CDC) Website regarding “good health habits” to place on signs and posters around the office.⁷ The other hidden threat is asymptomatic fowl, which present no signs or symptoms of disease. Dr. Robert Webster, a virologist for St. Jude Children’s Research Hospital calls the duck “the Trojan horse of this outbreak.”⁷ Several publications indicate that ducks are able to be infected with influenza, have no signs of disease, and are able to excrete large volumes of influenza virus in their feces.^{6, 8, 9} According to Dr. Webster, bodies of water with contaminated fecal matter infect many birds. This is “food for thought” to think about the next time you see someone feeding the birds at a local pond or lake. People will need to be mindful of our hygiene habits and of our extracurricular activities to help prevent the spread of influenza.

Fear and Motivation

Certainly, most of us are familiar with Maslow’s Pyramid of Needs. Abraham Maslow’s hierarchy of need theory states that human beings will first strive to meet physiological and safety needs before they worry about belongings and esteemed needs.¹⁰ According to this theory, and based on actual experience, during a pandemic, people will be more concerned about their family and their own health and well being than they will about whether their company will meet the business quarter sales returns. Since the overall mortality rate is currently over 50% for H5N1, fear will be rampant and good, factual communications will be essential - Figure 1, 2, and Table 1. Clear lines of communication will be paramount to stopping rumors and for providing people with correct, reliable information to make intelligent, rational decisions. Playing the “wait and see” game regarding a pandemic flu simply does not make good business sense. Dale Carnegie said, “When dealing with people, remember you are not dealing with creatures of logic, but creatures of emotion.”¹¹

Indeed, people’s behavior may be an important driver for the spread of a pandemic. Contemplate about how many people go to work when they do not feel well? Now think about how many children go to school and day care that are slightly under the weather and how these events could have a “snowballing effect” on the spread of influenza. Businesses will need to disseminate information, early on, regarding key facts about influenza, what you can do to prevent it, what are the signs and symptoms, and the locations of treatment centers. For example, companies may decide to provide their workers with safe working environments and perhaps pro-

vide living quarters for their employees and their families in the midst of a pandemic. In this situation, employees will need a site where they can have access to provisions and possibly medical resources. As part of the preparation process, businesses, local authorities, and care providers need to determine who they should be teaming with to help the surrounding community in the face of a pandemic flu threat.

Knowledge and Planning

As Louis Pasteur once said, “Chance favors the prepared mind.”¹² According to the WHO, companies should be identifying pandemic teams, developing plans, and running drills now to ensure preparedness.¹³ The WHO has developed a tracking system for the potential warning signs of pandemic flu - Table 2. As you can see by the table, the world is currently in Phase 3 of the Pandemic Alert Period - there is a novel influenza strain infecting humans with no or very limited human-to-human spread of the virus - Table 2. As also suggested by a recent Harvard Business Review article, now is the time in which companies should develop risk mitigation plans and run practice drills to elucidate any problem areas.¹⁴ Let’s use Y2K as an analogy. From a business standpoint, the salary for a computer programmer well before Y2K was decent. The cost-benefit for companies to hire and come up with a possible solution for Y2K was good if the company did not wait until the last minute. As we got closer and closer to Y2K, the cost to hire a computer programmer became astronomical due to the basic law of supply and demand. Even though the worst fears about Y2K never happened, we can still learn something from this event. *There is no financial or business benefit in waiting until the last minute to prepare* and you cannot adequately prepare for this type of contingency when it is already upon you. If a pandemic influenza does not materialize this year, it could come another year or some other type of epidemiological threat in the future could have the same effect. Experts have indicated that some type of pandemic occurs globally on a regular cycle and the next

pandemic is essentially inevitable.

Remember, that forewarned is forearmed. Companies can “arm” themselves with the knowledge of pandemic influenza and guides that can be found on government Websites, such as the WHO, CDC, and PandemicFlu.gov. Organizations need to explain and put in place appropriate policies regarding possible flexible leave procedures, working or telecommuting from home, or from remote sites, flex-time, short-term disability policies, quarantine scenarios, day care arrangements, sick leave, etc., prior to the organization being immersed in a pandemic or other type of epidemiological threat. If every problem presents an opportunity, then the threat of a pandemic will allow companies to show how much they care and value their employees.¹⁵ As mentioned earlier, companies could provide safe living quarters for their employees and their families during a pandemic. Companies also could have stocks of anti-viral medication available for their critical staff.

Having a plan for possible pandemic influenza, if done properly and kept up to date, will prepare a company or an organization for influenza or for any other epidemiological threat that may occur in the future. Businesses will need to identify a risk management group for pandemic influenza now and add pandemic preparations to their business continuity plans. Nitin Nohara, the Richard P. Chapman Professor of Business Administration at Harvard Business School, thinks of the threat of a pandemic as “*survival of the adaptive.*” She suggests that companies need to identify decision makers during a pandemic that are able to apply “new ways of problem solving in an unpredictable and fast-changing environment.”¹⁶ As we know, people in the pharmaceutical/biotech industries are highly innovative, they often “think outside the box,” and they can troubleshoot problems in real time. These skills will be required and in high demand for business continuity and for adaptation during a global pandemic. Another way to think about how to be prepared for a pandemic is to consider the analogy of marine expeditionary

Country	2003		2004		2005		2006		TOTAL	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Azerbaijan	0	0	0	0	0	0	8	5	8	5
Cambodia	0	0	0	0	4	4	2	2	6	6
China	0	0	0	0	8	5	11	7	19	12
Djibouti	0	0	0	0	0	0	1	0	1	0
Egypt	0	0	0	0	0	0	14	6	14	6
Indonesia	0	0	0	0	17	11	37	31	54	42
Iraq	0	0	0	0	0	0	2	2	2	2
Thailand	0	0	17	12	5	2	0	0	22	14
Turkey	0	0	0	0	0	0	12	4	12	4
Viet Nam	3	3	29	20	61	19	0	0	93	42
TOTAL	3	3	46	32	95	41	87	57	231	133

Total number of cases includes number of deaths. WHO reports only laboratory-confirmed cases.

Table A. Cumulative number of confirmed human cases of avian influenza A / (H5N1). (Source: WHO, 20 July 2006).

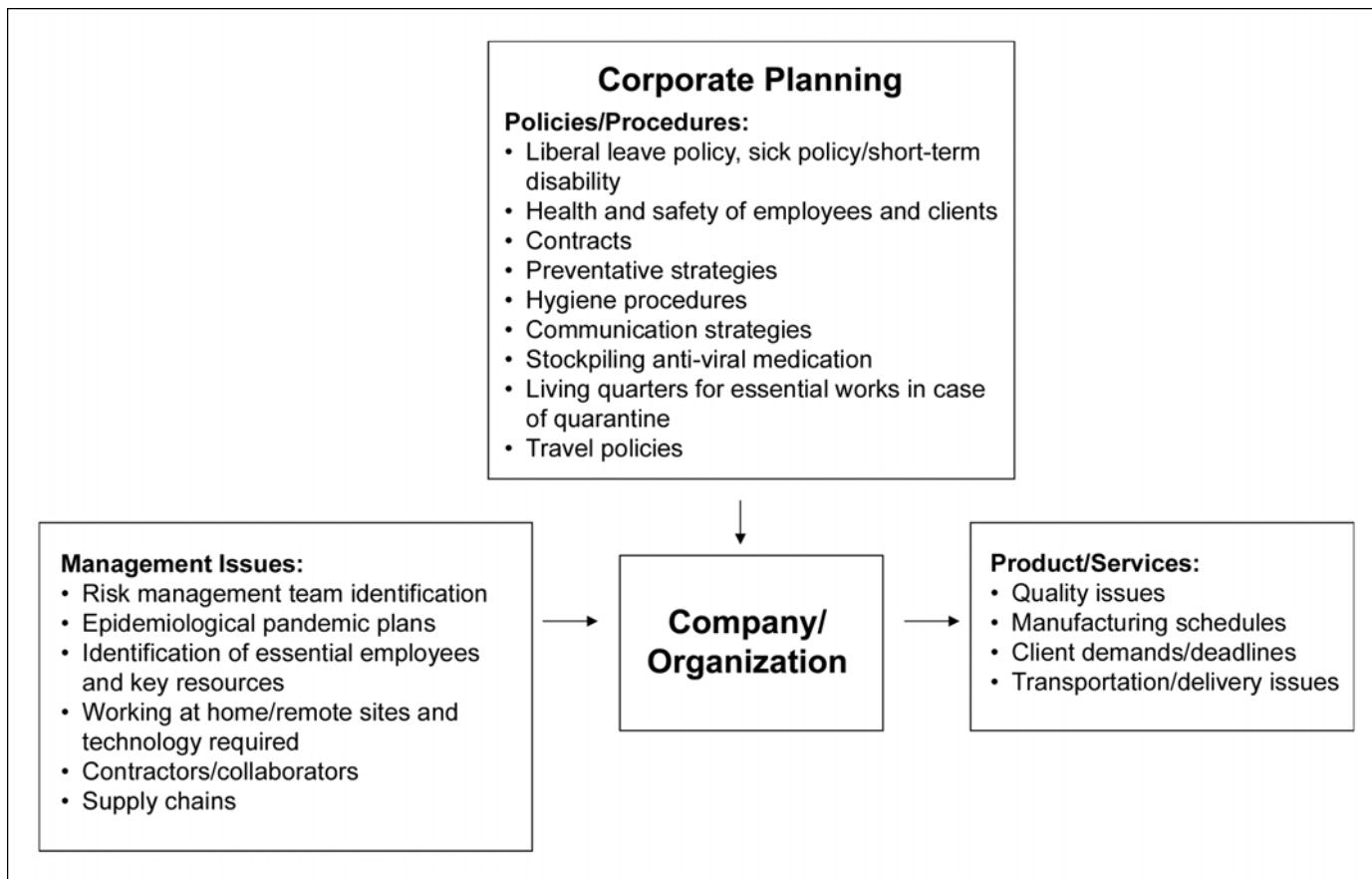


Figure 3. Examples of some of the issues that companies will need to consider when planning for a pandemic.

forces, suggested by Nitin in the May 2006 Harvard Business Review. The marines are highly effective in mission critical situations because they not only practice as a team, but everyone on the team can *lead* the team.

In May 2006, US President George Bush released the National Strategy for Pandemic Influenza – Implementation Plan. The President’s plan outlines more than 300 critical actions that may be executed to address a pandemic influenza. There are three main objectives to the plan: protect employees; maintain essential functions and services; and lines of communication. The plan also advises companies and individuals to access plans and check lists that are available on the CDC, WHO, and pandemic.gov Websites. An Emergency Budget Request of \$7.1 billion over the span of several years has been submitted to Congress. In the 2006 fiscal year, \$3.8 billion was appropriated to help fund the following activities: stock piling anti-viral medication; expand domestic vaccine production; expand surveillance capabilities domestically and internationally in humans and animals; and investments in development of risk communication strategies.

In addition to the President’s plan, the US Food and Drug Administration (FDA) developed a new team in response to a possible pandemic influenza. In the fall of 2005, the FDA announced the formation of a Rapid Response Team (RRT). The RRT would help ensure the following: an adequate amount of anti-viral medication is stockpiled in the event of a pandemic influenza; support the design and implementa-

tion of clinical trials of novel treatments of avian flu; and assist and evaluate studies using new technologies for vaccine development. Andrew von Eschenbach, MD, Acting FDA Commissioner, stated that the RRT would allow complete review of a drug in six to eight weeks.¹⁷ The FDA is dedicated to ensuring that the US has enough medication to combat pandemic influenza.

Watson Wyatt Worldwide, a global human capital firm, conducted a survey and found that 15% of companies have pandemic influenza plans in place in the United States, 11% in Europe, 10% in Canada, and 9% in Latin America.¹⁸ However, 32% of companies in Asia-Pacific had pandemic plans. Another surprising finding was that one in five companies are not alarmed at all about pandemic influenza. There was an increase in the percentage of companies considering a pandemic plan: 52% in Asia-Pacific, 48% in the United States, 47 % in Europe, 44 % in Latin America, and 42 % in Canada.¹⁸ An important question to ask is; why are the majority of companies just considering having a plan and are not devising a plan?

Collaboration will play an important role in strategic business planning for a pandemic flu event. A combination of cross training, an adaptive risk management group, and support by all employees and contractors will aid in honing the effectiveness of a plan. Companies will need to do a “self evaluation” and think about what keeps them running and successful, what are their supply chain issues, who are their critical staff, and how they can serve their clients during a

pandemic - Figure 3. Does your company have sufficient back-up supply relationships? Bear in mind that there is a difference between *conception* of a plan and the *execution* of a plan. Practice drills will need to be run to illuminate holes or possible problems with your plan. Edward de Bono said, "We may need to solve problems not by removing the cause, but by designing the way forward even if the cause remains in place."¹⁹

The Business Case

Having considered some of the salient scientific and technical factors auguring for why organizations should have a well-developed epidemiological plan, the next step is a balanced and sober analysis of the strategic and business management issues. To play this game effectively, the organization should have both an "offense" strategy and a developing capability for *advancing* the business interests of the organization and for capturing the desired opportunities that arise; and a "defense" that includes a preventative strategy for *protecting* the business continuity and cushioning the enterprise by providing tools and techniques for managing or coping with the contingencies.

Among the advancement opportunities, the opportunity to develop sales through meeting anticipated and likely market demands for products and services that would result from an epidemiological pandemic, or even resulting from the fear and anticipation of such a pandemic scenario, is certainly a key consideration. However, a number of other benefits also should be considered. For example, the research developments associated with response to the specter of an epidemiological pandemic also may have significant spin-off benefits for other market segments. In addition, the robust operational flexibility that can be achieved through an investment in well-designed epidemiological pandemic planning programs can pay significant benefits and dividends.

On the defensive or preventative side, there may be an equal number of opportunities for strengthening supply chains, taking advantage of contractual lead times, and identifying key resources for optimal responses to various scenarios. In other words, with proper planning, the defensive or preventative strategies that would pay big dividends during a major crisis scenario also may enhance normal, day-to-day operations. Similarly, the organization may find greater success and viability during a *minor* crisis scenario, provided that these objectives are considered and balanced by the epidemiological team during planning and implementation phases.

Spring Training and Practice Drills

The case for the tangible benefits of targeted and effective training programs has been made in many places, and a further discussion of these benefits is not needed here. However, epidemiological planning presents a new perspective on this well-known phenomenon.

Training for epidemiological preparedness and business continuity provides an opportunity to develop and ingrain genuine strengths and adaptability into the organizational culture. For example, not only does cross-functional training

help build teamwork and productivity, but also a new vitality can result from overcoming epidemiological pandemic fears, and replacing these with solid factual information, pervasive communications channels, beneficial plans, and constructive procedures.

If the matter is properly managed, the time and resources spent on epidemiological planning and preparation will not be wasted if the exact scenario or planned for event does not occur. First, some will believe that some type of epidemiological pandemic event is simply inevitable and being prepared for this type of scenario is just good business. Indeed, many experts in the field already agree with this assessment. Second, as alluded to above, a properly designed epidemiological plan will pay benefits for a *variety* of contingency scenarios, and such planning can help with maintaining smooth business continuity despite minor "blips" or "hiccups" over time. Indeed, one can argue that proper epidemiological planning and preparation will actually *convert* a larger tsunami crisis into a more manageable "ripple" that is far less disruptive.

Building your Bench

Winning teams know that a strong bench wins championships. When a team has a strong bench, the bench players will keep the team in contention, even when the starters are out of the game.

Tackling a problem such as epidemiological preparedness has the ability to build that bench strength. A global pandemic will not honor or abide by the organizational chart nor stop at the doors of the executive suite. The need for cross-functional training and for backup leadership is as strong in this situation as it is on the battlefield or in professional sports.

Business continuity will depend on flexibility and adaptive creativity. Yet building this flexible character also will create additional benefits for the organization. When key people have a strong, flexible understanding of the functional requirements of their co-workers and supervisors, they will become more proactive and productive; and fewer items "fall through the cracks." This type of thinking also can be applied to the supply chain and to product delivery. The result: Even normal, day-to-day operations become more effective and

Interpandemic Phase New virus in animals, no human cases	Low risk of human cases	1	
	Higher risk of human cases	2	
Pandemic Alert New virus causes human cases	No or very limited Human-to-human transmission	3	
	Evidence of increased human-to-human transmission	4	
	Evidence of significant human-to-human transmission	5	
Pandemic	Efficient and sustained Human-to-human transmission	6	

Figure 4. The World Health Organization's description of the phases leading up to a pandemic. (Source: WHO).

What is Influenza?

Influenza is an obligate parasite, which cannot reproduce by itself and requires a host to replicate. There are three types of influenza: Type A, Type B, and Type C. Type A Influenza's can infect a variety of hosts, including birds, swine, horses, and humans. Type A and Type B are responsible for the seasonal flu outbreaks and they have the ability to genetically mutate to avoid the host's defense mechanisms.⁴ We are probably all too familiar with the common flu symptoms: fever; sore throat, coughs, chills, and muscle aches. On the other hand, Type C influenza is responsible for non-seasonable mild illness in humans.

Type A Influenza

Type A Influenza strains are named based on the subtype of two important surface glycoproteins: hemagglutinin and neuraminidase. Hemagglutinin (HA) has 16 subtypes, H1-H16, and allows the virus to attach to and enter a host cell. Neuraminidase (NA) has nine subtypes, N1-N9, and allows the mature virus to escape from the host cell after replication. Humans and swine are natural reservoirs for the following influenza Type A subtypes: H1, H3, N1, N2, and H2 (humans only). However, birds are a natural reservoir for all subtypes of Influenza Type A. The H5N1 strain of influenza (Type A) is the first known case of an avian flu being responsible for directly infecting humans.

Medical Resources for Influenza – Vaccines and Anti-Viral Medication

What about vaccines and anti-viral medication? The annual flu vaccine is a trivalent vaccine – made up of three different influenza strains. Normally, the flu vaccine is composed of two Type A Influenza strains and one Type B Influenza Strain. Dr. Joe Duarte, a financial writer, stated that Novavax has two flu vaccines in early stages of development.²¹ However, we will need to isolate the exact strain of pandemic influenza from patients and then it will take between six to nine months to have the effective pandemic flu vaccine ready for mass vaccination. On the other hand, Gilead and Roche and Glaxo SmithKline make Tamiflu and Relenza, which are two antiviral neuraminidase inhibitors. Neuraminidase inhibitors appear to have fewer incidences to drug resistance than the other class of antiviral medication, M2 ion channel inhibitors.

Vaccines are currently manufactured through the use of chicken eggs. It takes approximately 300 million eggs to produce 90 million doses of trivalent flu vaccine a year.⁴ If we have to slaughter chickens to remove the spread of H5N1, how are we going to have enough eggs to generate a vaccine against H5N1? Luckily, there are also companies working on vaccines that are not dependent on chicken eggs. The U.S. Department of Health and Human Services (HHS) awarded more than one billion in contracts in May, 2006 for the development of cell-based vaccine technology to the following companies: Solvay Pharmaceuticals (\$299 million), GlaxoSmithKline (\$275 million), Novartis Vaccines and Diagnostics (\$221 million), MedImmune (\$170 million), and DynPort Vaccine (\$41 million).²² HSS also is expected to award more contracts for the construction of new vaccine facilities or expansion/redesign of existing facilities and for ways to reduce the amount of vaccine that is required for protection.

more adaptable to business fluctuations and to unanticipated circumstances, honing that competitive edge.

Appealing to the Crowd

Sound preparation for an epidemiological contingency also can appeal to customers and stakeholders of the organization. Being prepared for appropriate contingent scenarios is perceived as prudent business practice. Such planning will not only *ensure* a continuity of operations, but also will *assure* your customers and stakeholders that you are solidly “on top of your game.”

Backup plans, work-around options, and provisions for strength and stability of operations will give your customers and your stakeholders' confidence in your organization. That confidence translates into sales, investor support, and advantageous business alliances. Conversely, not being properly prepared for the dreaded contingent scenario, especially if the scenario actually occurs, can undermine public confidence in your organization, and these effects can be long-term or even irreversible. Being ready also means being competitive, stable, and sustainable.

Timing is Everything

Should the pharmaceutical and bio-technical industries be concerned about the threat of a pandemic flu? Answer: industry professionals should be aware of the issues and should be prepared to respond appropriately to this threat.

Ask yourself whether your company or organization is fully and adequately prepared for a pandemic flu or for other, equally threatening epidemiological contingencies that may occur. As indicated throughout this article, *now* is the time to identify risk management teams, to devise comprehensive epidemiological pandemic preparation plans, to train employees, and to run practice drills for purposes of assuring business continuity. We have made many advances as a society since the last major pandemic, and our knowledge and the availability of new technologies can be used to our advantage. On the other hand, modern technology, including global trade and intercontinental air travel, can rapidly spread diseases and illnesses around the world with no regard for national boundaries. Essentially, this is the flip side of the burgeoning globalization mega-trend of recent decades.

In closing, consider this thought on globalization from Stas Margaronis, “The time has come for Europeans and North Americans, who have for years advocated globalization in the outsourcing of production, to begin practicing the need for globalization in the saving of human life.”

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This article presents an overview of the differences between regulatory authorities between first world and third world countries, and the problems and solutions applicable to third world countries.

Pharmaceutical Regulatory Issues – Observations from Africa

by Deryck Smith Pr. Eng.

Regulatory bodies in developing countries face challenges very different from those of First World countries. These bodies are endeavoring to raise local standards to compare favorably with those of Europe and the US. This will result not only in the production of high quality products, but it also will result in the economic spin-offs so vital to the survival of these growing economies. Engineers in these countries find themselves having to come to grips with the dilemma of trying to design facilities which will comply with global standards, while having very limited local funding available. In addition to engineering skills and a sound knowledge of regulatory requirements, pharmaceutical engineers in Africa need considerable ingenuity to find solutions which will satisfy all the players in the industry.

In South Africa, competent pharmaceutical engineering consulting services are available, as well as contractors experienced in the implementation of pharmaceutical projects. Companies experienced in conducting the required testing for validation of facilities, such as particle counts, filter integrity tests, and bacterial counts, also operate locally.

Africa has recently seen a dramatic advance in the regulatory requirements for pharmaceutical manufacturing facilities. Previously, countries had either no official standards, or locally developed standards. Now the general trend is to adopt international standards, such as those developed by the Pharmaceutical Inspection Cooperation Scheme (PIC/S).

The difference between African regulatory standards and European or US regulatory standards lies not so much in the documentation,

Tanzania WHO Training Group.





Barrier isolator cleanroom.

but in the application of the regulations. It would be fair to say that most African regulations are based on existing EU or US regulations; therefore, they are fairly similar. There obviously are differences, for example, the South African National Medicines Regulatory Authority (SANMRA) Guideline requires 20 air changes per hour to achieve a Grade D condition, whereas the PIC/S GMP Guideline stipulates that the air changes should be related to the room configuration and function. Another difference between the above two Guidelines is the permissible number of $5\mu\text{m}$ particles for Grade A and B. PIC/S allows one particle per m^3 , whereas the SANMRA stipulates this should be zero. This discrepancy also is evident in other national MRAs and was a topic of discussion at the Global Regulatory GMP Conference in Prague in September 2005.

The majority of African pharmaceutical facilities are solid dosage or liquids plants, and there are very few sterile facilities and API plants. Regulatory documentation is fairly prescriptive in the requirements for sterile plants, but there is not much information on the requirements for solid dosage and liquid plants and there lies the problem with the differences in interpretation. The WHO has recently released a document titled "Supplementary Guidelines on Good Manufacturing Practices for Heating, Ventilation, and Air-Conditioning (HVAC) Systems for Non-Sterile Pharmaceutical Dosage Forms," which should assist regulatory inspectors with the requirements and norms for these plants.

The lack of inspector understanding and training is discussed in a WHO document recently released. The document titled, "Medicines Regulatory Authorities: Current Status and the way Forward," cites the results of surveys conducted in African countries. Some of the problems encountered are listed below:

- 90% of the Medical Regulatory Agencies (MRAs) lack the capacity to carry out medicines regulatory functions; therefore, they cannot guarantee the quality, efficacy, and safety of medicines.

- 84% of MRAs have inadequate staff. In addition, the staff lacks the qualifications and experience needed to perform all MRA functions.
- External expertise is solicited in 58% of the cases.
- 42% of MRAs issue or renew licences for the various practitioners without checking or referring to the records of inspection reports.
- 63% of MRAs are unable to evaluate new medicines due to inadequate resources, and in the case of vaccines, 87% of MRAs are incapable of evaluating them.

From the above, it is obvious that remedial steps are required; and in the document, the WHO puts emphasis on having clearly defined missions, training, funding, organizational structures, adequate documentation, and resources, etc.

In South Africa, the National Medicines Regulatory Authority within the Department of Health, has applied to become a member of PIC/S, and has undertaken energetic training of their inspectors in all spheres of the industry. When South Africa becomes a member, they will join approximately 29 other member countries, which have the benefit of operating with an international standard. Most national standards have basically the same intent; that of ensuring good quality pharmaceutical products. However, the interpretation of these standards by inspectors often varies. The advantage of being a PIC/S member is that common training is provided and uniform interpretations of guidelines should result. This should make life easier for the manufacturers as well, as they will be graded on a common standard. When conducting an inspection, one often hears the manufacturer claiming regulatory bodies A and B have approved their facility and that regulatory body C finds fault. The adoption of international standards would help alleviate this sort of problem. However, the application of these standards by the inspectors would need to be harmonized. Different interpretations of standards frequently leave a lot to be desired; therefore, the training of inspectors is of paramount importance.



Barrier isolator cleanroom (empty).



Barrier isolator cleanroom (operational).

Local pharmaceutical manufacturers in South Africa now have to comply with the PIC/S standard, in anticipation of SA being granted PIC/S membership. However, in some cases, other international standards need to be considered in order for these companies to be able to manufacture under license from large international players in the pharmaceutical industry, and in order to be able to export to Europe and the US. Consequently, the industry in Southern Africa, and Africa as a whole, is being subjected to tremendous pressure to raise standards. In addition, GMP requirements are constantly changing and evolving. As a result, one finds that facilities which were considered to be state-of-the-art manufacturing plants 10 years ago are now no longer GMP compliant. Bodies such as the WHO have undertaken to train pharmaceutical inspectors in developing countries, and have developed training guides and presentations which regulatory bodies can source and use in further training. These have been developed particularly for inspectors in developing countries, and are easily available on the WHO Web site. The training, specifically pertaining to facility design, includes modules on cleanroom criteria and standards, environmental control systems (HVAC), building layout, facility finishes and materials, water for pharmaceutical facilities, and validation of these systems. Where some inspectors had previously never seen an air handling unit, they are now familiar with the basics of air systems.

Facility Design

Pharmaceutical facility projects being undertaken in developing countries mainly take the form of upgrades of existing facilities, and not many green-field facilities are being undertaken. In most cases, the upgrading of these old, non-compliant facilities, results in having to find compromise solutions with regard to layout, product flow, air pressures, and air-flow. A considerable amount of ingenuity is required in order to come up with acceptable layouts within the confines of the existing structure. In most instances, a company has expanded from a small beginning, and as it has grown, it has expanded the facility into whatever space is available. This seldom results in a logical and orderly staff and product flow. Rectifying such a layout without radical changes, which the

client can seldom afford, makes the task of creating a GMP compliant design far more difficult than planning a new facility.

Clients frequently do not fully grasp some of the concepts of product flow and staff flow, and what packing materials, shippers, pallets, etc., are allowed in the different areas. For example, once zones are segregated, such as Primary and Secondary Packing, there is often a necessity for double handling of products. This involves activities such as moving materials from wooden pallets to GMP pallets, double bagging of bottles to avoid taking shippers into Primary Packing areas, creating wipe-down airlocks for Primary Packing materials, etc. These activities are obviously time-consuming, and the manufacturer is usually resistant to these changes, which have an impact on productivity. However, in order to ensure GMP compliant production, these steps become mandatory.

In a developing country, one faces a dilemma when a factory is closed down because of non-compliance; it results in job losses and the ensuing social problems. Until recently, because of the high capital costs of upgrading a facility, regulatory bodies have been relatively tolerant to companies which have started to slowly upgrade their facilities in phases; over a number of years. However, for these bodies to achieve or maintain their status as members of, for example, PIC/S, this is no longer possible, and delinquent companies are being shown little mercy and being forced to upgrade or cease the manufacture of pharmaceuticals. African pharmaceutical companies are far from the technology hubs and it is more difficult for them to attend conferences to keep up with current trends. The pharmaceutical industry is dynamic and standards are constantly changing to improve the safety of medicine. If a company fails to take account of this, and implement changes as new trends develop, the facility will steadily become outdated and non-compliant.

Large amounts of donor funds are being channelled into countries such as Zimbabwe, Nigeria, Uganda, et al. Not only are these helping to fund pharmaceutical plants, but also are being utilized for the research of vaccines. An example of this can be seen in Zimbabwe, where all four major pharmaceuti-



Dispensary pre-staging.



Production passage.

cal manufacturers are currently either in the processes of upgrading or are in the planning process to upgrade.

Research into vaccines also is on the increase with a number of Bio-Safety Level (BSL) laboratories of varying levels being built. A new BSL 4 laboratory is currently being erected in Johannesburg with local engineering expertise being utilized for this challenging installation. Strict validation procedures and documentation will be locally prepared.

Although there are now increasing numbers of facilities of a very high standard in Southern Africa, it is difficult to compare these with facilities in First World countries, where funding seems to be more readily accessible. However, with regard to product flow, staff flow, air handling plant, and building finishes, some of the upgraded facilities in South Africa need stand back for no one. The cost of erecting these facilities in South Africa is significantly lower than in Europe and the US. This is attributed to the significantly lower labor costs and making use of local materials, rather than imported materials.

Building finishes for facilities in developing countries also create a challenge on both new and upgraded facilities. Cleanroom modular panelling is not available in African countries, and the importation cost from Europe or the US is prohibitive. Consequently, suitable finishes need to be created from the materials locally available.

In Third World countries, facilities tend to manufacture a large range of products, but in fairly small batches. This is as opposed to developed countries, where Centers of Excellence

are created and these plants may manufacture only one product. In a multiple-product facility, the prevention of cross-contamination plays a far greater role and can greatly inhibit productivity.

The misinterpretation of GMP guidelines by manufacturers and engineers often leads to anomalies in a manufacturing plant, when the basic guideline is applied without understanding the reason behind the guideline. For example, one penicillin plant had a production area operating at a negative pressure of 100 Pa, which resulted in excessive infiltration of contaminated ambient air. The manufacturer reasoned that a negative pressure was required; therefore, “played safe” by increasing the pressure to an unreasonable level, whereas a pressure of -30Pa would have been quite adequate to provide containment (without excessive infiltration).

Similarly, some facilities have opted to implement extremely high standards, in one aspect, to the extent of being overkill, and ignored other important GMP criteria. A balanced approach to all GMP criteria is required. Staff discipline is frequently the downfall of a well designed facility.

One aspect of compliance which is new to many local companies is that of Validation of the facility, in particular the validation and qualification of the environmental control systems, electrical installations, and architectural finishes. Although multi-national manufacturers comply with this requirement and prepare the required detailed validation documentation, local manufacturers are always stunned at the costs involved in this time consuming task, and the copious documentation required. Clients are generally aware that validation is required of pharmaceutical manufacturing equipment, but validation of environmental control systems and other services is foreign to them. After being inspected by a regulatory authority, manufacturers have often frantically requested that their plant be validated, because the regulatory authority has asked to see the documentation, and they cannot comprehend when it is explained that it would be a fruitless waste of money, as the validation documentation would merely confirm that their plant doesn't work. A facility needs to be made GMP compliant before it can be validated. However, larger manufacturers are requesting training and education in areas of general cleanroom principles, air handling systems, building finishes, validation, etc. The scene is being set for global players in the industry to take advantage of the lower capital costs, and increased GMP standards of facilities in developing countries. They are beginning to utilize the expertise being developed in these countries for the manufacture of many of their products.

In conclusion, the sustainability of the African pharmaceutical industries lies largely with coming to grips with current trends, regulatory requirements, and training.

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About the Author



Deryck Smith is a registered Consulting Engineer with 40 years of experience in the field of ventilation and air conditioning, the last 16 of these being devoted exclusively to cleanroom technology. He is considered to be a leading expert in this field in South Africa, and has achieved some international recognition. He has, on occasion, worked as a

Consultant for the World Health Organization, attending related Meetings of Experts in Geneva. Smith has conducted training on their behalf for pharmaceutical inspectors from developing countries and has assisted with inspections. In addition, he has assisted with the preparation of an HVAC Guide for Pharmaceutical Inspectors. While Smith is respected as a leader in South Africa in the area of environmental control systems for pharmaceutical manufacturing facilities, he also consults on issues relating to HACCP accreditation in the food and beverage industries with reference to airflow, staff, and product flow. Hospitals and medical facilities also fall within his field of expertise. Smith sits on the South African National Standards (SANS) Committee for Hygiene Standards in the Food and Beverage industries. He has conducted extensive training on cleanroom principles for various regulatory bodies, including the SA National Medicines Regulatory Association, industry organizations such as the SA Association of Food Science Technology (SAAFoST), and large local retail companies. He has presented a number of papers at various conferences (such as the International Federation of Hospital Engineers, the SA Association Pharmacists in Industry, et al), has published various papers, and has been featured in many journals and other publications (The British Food Journal, et al). Deryck qualified as a Mechanical Engineer at the University of Pretoria, South Africa, and is a registered Professional Engineer with the Engineering Council of South Africa. He is also a member of ISPE, the SA Association of Consulting Engineers, SA Institute of Mechanical Engineers, the SA Federation of Hospital Engineers, and is a Custodian member of SAAFoST. He can be reached by tel: +27 12 367-5980 or e-mail at: derycks@ssi.co.za.

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This article presents the new joint Authority established to replace the Australian Therapeutic Goods Administration (TGA) and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe).

Proposed New Joint Regulatory Authority for Australia and New Zealand

by Bob Tribe, ISPE Asia-Pacific Regulatory Affairs Advisor

Introduction

The Australia and New Zealand governments have agreed to establish a trans-Tasman therapeutic products Authority which will replace the Australian Therapeutic Goods Administration (TGA) and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe). The new joint Authority will be known as the Australia New Zealand Therapeutic Products Authority (ANZTPA) and is expected to commence operating in late 2007.

Objective of ANZTPA

The objective of ANZTPA is to safeguard public health and safety in Australia and New Zealand by maintaining and administering a joint scheme, consistent with international best practice for the regulation of the quality, safety, and efficacy, or performance of therapeutic products and their manufacture, supply, import, export, and promotion.

This will be achieved through a framework that:

- applies a level of regulation that is commensurate with the potential risk to public health and safety posed by therapeutic products
- balances these risks and the potential benefits to be obtained by users from the availability of these products in Australia and New Zealand
- ensures consumers have sufficient, accurate information to enable them to select and use therapeutic products safely and effectively

- assists New Zealand and States and Territories of Australia to adopt a uniform approach to controlling access to therapeutic products
- as far as possible, harmonizes requirements with overseas regulators of equivalent standard

Scope of Activities

The authority will regulate the import of therapeutic products into Australia and/or New Zealand, the export of therapeutic products from Australian and/or New Zealand, and the supply, manufacture, and promotion of therapeutic products in Australia and/or New Zealand.

The authority will do this through:

- pre-market evaluation and assessment of therapeutic products
- product licensing
- post-market monitoring and surveillance
- audit and licensing of manufacturers
- setting of standards

The different categories of therapeutic products to be regulated and controlled by the authority will be as follows:

- prescription medicines
- over-the-counter medicines, including sun-screen products

- complementary medicines, including nutritional supplements, herbal medicines, traditional medicines, vitamin products, aromatherapy products, homoeopathic medicines
- human blood and blood components
- cellular and tissue therapies
- medical devices, including in vitro diagnostics, sterilants, instrument-grade disinfectants
- other products meeting the definition of therapeutic product

The joint Authority will be fully funded from fees and charges paid by the industry for the evaluation and approval of their products and the audit and licensing of manufacturers. There will be a three-year transition period to enable companies to meet the new regulatory requirements.

Regulatory Framework

The new Authority will replace the Australian TGA and Medsafe, and will be accountable to the Australian and New Zealand governments. It will have a distinct legal identity and be recognized in law in both Australia and New Zealand. It will assume responsibility for the regulatory functions currently undertaken in both countries.

The authority will be overseen by a two-member Ministerial Council comprising the Australia Minister of Health and the New Zealand Minister of Health. The authority also will have a five-member Board. The Board will be responsible for the strategic direction and financial management of the authority. One of the Board members, the Managing Director, will be responsible for regulatory decisions about therapeutic products and for the day to day management of the authority. The Board and the Managing Director will be appointed by the Ministerial Council.

The framework for the regulatory scheme administered by the authority has been set up under a Treaty and will be implemented through Acts of Parliament in both countries, a single set of Rules made by the Ministerial Council, and technical Orders made by the Managing Director. These Acts, Rules, and Orders will replace the existing Australian Therapeutic Goods Act, its regulations and Orders, and the existing New Zealand Medicines Act 1981 and its Regulations.

Benefits

The new authority will have a number of benefits for both countries, including:

- assisting in the creation of a single market for therapeutic products
- facilitating trade and reducing compliance costs by replacing dual regulatory processes with harmonized regulatory requirements
- strengthening each country's regulatory capacity to meet a new wave of innovative therapeutic products which are being driven by emerging technologies and globalization
- ensuring consumers have early access to new products entering the market, while maintaining confidence in public health and safety

Consultation


Since the late 1990s, extensive consultation with industry, health professionals, and consumer groups has taken place on the establishment of the new joint Authority. Discussion documents and other reports and documents designed to keep stakeholders informed of developments on the establishment of the Authority are available on the ANZTPA Web site (www.anztpa.org). Some of the documents released during the recent consultation phase (lodgment of comments on these documents closed on 15 August 2006) included:

- Draft Medicine Rule
- Proposed Grouping Order for Medicines
- Draft Guideline on Transition Provisions for Product Licensing
- Draft Medical Device Rule
- Draft Administrative Rule
- Proposed Fees and Charges
- Proposed Medicines Manufacturing Principles
- Plain English Guide on the draft Rules

About the Author



Bob Tribe is ISPE's Regulatory Affairs Advisor for the Asia Pacific, based in Canberra, Australia. He joined ISPE from the Therapeutic Goods Administration (TGA)

in Australia, where he served as Chief GMP Auditor for 23 years. During that time, he not only enhanced the TGA's reputation as a leading GMP regulator internationally but also held leadership positions with the Pharmaceutical Inspection Cooperation Scheme (PIC/S), serving as vice chairman in 1998-1999 and chairman in 2000-2001. Recently, Tribe founded a company to provide consulting to GMP regulatory authorities around the world. 

This article demonstrates how Quality by Design (QbD) concepts can be applied to process, data, and equipment systems and addresses the implications of FDA's Process Analytical Technology (PAT) guidance.

Quality by Design, Validation, and PAT: Operational, Statistical, and Engineering Perspectives

by Ron Branning, Lynn Torbeck, and Cliff Campbell

Introduction

Dr. Janet Woodcock's exhortation (ISPE Annual Meeting, 7 November 2005) that 21st century life science manufacturers should be 'maximally efficient, agile, and flexible' and produce high quality drug products 'without extensive regulatory oversight' has been widely reported as a wake-up call to our industry. This article responds to this challenge by defining specific common-sense strategies that pharmaceutical engineers and technologists can adopt to reach those standards. In particular, it shows how Quality by Design (QbD) concepts can be applied to process, data, and equipment systems to generate self-validating outputs. It also addresses the implications of FDA's Process Analytical Technology (PAT) guidance with the emphasis on Right First Time.

This article presents the opinions of three authors with extensive experience in the areas of life science manufacturing, statistics, and engineering. While each section has been written independently, the article is a collaborative effort that offers a shared conclusion.

Section 1: Quality by Design (QbD) in Validation Planning

Introduction

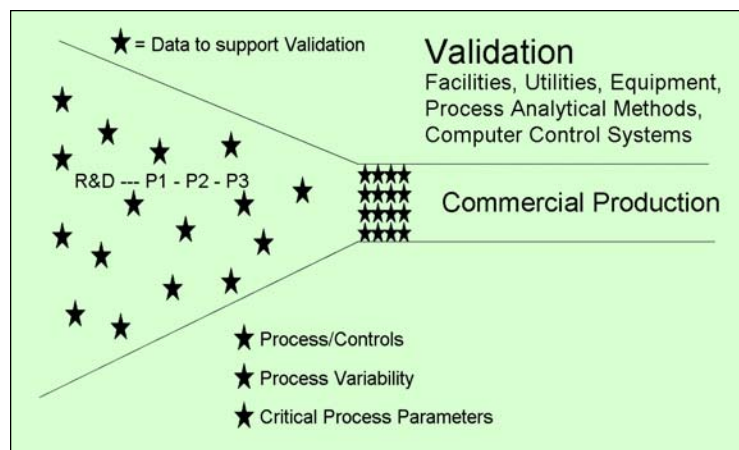
The mention of 'validation' evokes a range of responses among life science professionals, from anxiety and confusion to fear and wonder. The reason for this could originate from the FDA's 1977 definition 'validation is establishing documented evidence that a system will do what it purports to do.' The breadth of interpretation of this seemingly simple statement and the numerous attempts over the years to clarify it has only made matters worse. Regulators, practitioners, and consultants have all played a role in elevating validation to cult status.

The fact that the latest chapter in the continuing validation saga (FDA's PAT initiative to emphasize science and technological innovation) has only added to the confusion shows that the industry has failed to grasp the essence of FDA's 30-year-old validation message: manufacturers must understand their processes and control variability.

This section reviews current practice in a

number of validation areas and suggests how our efforts can be streamlined to save time, effort, and resources, while at the same time preserving and satisfying FDA's core expectations. A sample project is shown to illustrate how a QbD-driven approach, at organization level and in design and equipment construction, can simplify and add value to the validation process. A discussion on how

Figure 1. Integrated validation plan.



designing quality into our workflows delivers an integrated validation framework that serves the industry and satisfies current and emerging regulatory expectations.

QbD at the Organizational Level

Validation calls almost as many departments home as there are interpretations of what the term itself really means. The problem is not so much which department ‘owns validation,’ but more the need for cross-functional interaction and cooperation to prioritize, execute, and archive the validation workload. Departments with key roles within validation include:

- Process Development
- Engineering
- Manufacturing
- Quality

While any one of these can have overall responsibility for validation administration and oversight, each must be an active participant at the compilation and implementation level. Most discussions regarding what validation is and how to document it begin with ‘roles and responsibilities’ and end with ‘review and approval’ accountability. The discussions are endless and in many cases pointless. Validation is all too often the organizational reality of the paraphrase – ‘the validation debate has a thousand parents, validation is an orphan.’ Without such roles being explicitly defined, and in the absence of standard specifications and methodologies, the quality and value of our validation deliverables remains poor, often leading to avoidable and unnecessary duplication of testing. More significantly, it results in costly validation gaps that consume the scarce resources of industry and regulators alike.

Any manufacturing-related department can administer an effective validation system. Having a well defined system with clearly delineated roles and responsibilities is more important than its physical or organizational location. It is essential that the system defines where one department’s roles and responsibilities end and where another’s begins, from beginning to end of the validation life cycle. Specifically, it must provide for a double handshake across departmental boundaries to ensure that information flows in both directions and that the handoff is acknowledged by both the supplier and the recipient.

The following, very simple example of a tank order shows how QbD-driven criteria can be incorporated into the validation workflow.

1. A user specifies a tank, including its total and working volume, temperature control target and range, pH requirements, and mixing conditions.
2. Process Engineering reviews the user requirements, finds a certified designer and fabricator with appropriate experience, and prepares a specification for a bid proposal.

3. Process Development reviews the user requirements, the process engineering specifications, and the process technology data to ensure that the user and process engineer have defined the vessel appropriately.

4. Quality Assurance compares the documentation with the approved tank standards for the intended use and signs off on the user requirements and specifications package, returns it to Engineering for design, and notifies all the stakeholders of the approval.

QbD in Construction

Tank fabrication is based on the availability of a formally approved and qualified design. Clear specifications that set out not only the type and materials, but also the functional and environmental constraints on its intended use, ensure that the fabricator delivers an asset that is fit for use and is Right First Time. If the specifications are unclear, a tank may have a total volume that was intended to be the working volume – 5,000L instead of 6,000L. An incomplete specification might result in a tank that has thermowells and probe positions in locations that are expedient in terms of fabrication and installation, but that fail to satisfy more important operational and maintenance requirements.

Putting it All Together

The data to support validation is collected throughout process development as each department applies its requirements. Specifications for the equipment type (open or closed vessel) and materials of construction (glass or stainless steel) are determined at the very beginning. The scale-up to clinical, and ultimately commercial, quantities in turn dictates facility and utility requirements as well as improved analytical tools and process/computer controls. The objective of R&D and Clinical Studies is to bring safe and effective products to market. The goal of the Process Development group is to take a small scale process with wide variability and bring it into a state of control for large scale commercial production.

At each step, valuable information is collected in lab notebooks and on analytical data sheets. All this data can be used to identify sources of variability and critical process parameters (time, temperature, pH, flow rate). The challenge for Validation is to glean all the process variability knowledge from the development process and apply it to controlled, statistically valid experiments that result in a robust, well monitored, well analyzed, and controlled process producing consistent product.

Developing and applying agreed industry standards for specification and validation would:

- yield reliable, self-validating outputs at each stage of the development process
- eliminate redundancy in testing and documentation
- eliminate ambiguity in specifications
- eliminate gaps and overlaps in departmental roles and responsibilities

- allow regulators to audit the standards rather than individual tests
- save companies time and resources
- adapt readily to innovation

Figure 1 shows the scattered variable data points in development that are brought into tighter alignment and control in commercial production.

Lynn Torbeck makes a persuasive argument in Section 2 of this article for using Design of Experiments (DOE) (conducting and analyzing statistically designed tests to evaluate the factors that control the value of a parameter or group of parameters) to identify Critical Process Parameters (CPPs). The earlier that DOE can be used within process development, the quicker and less expensively data can be gathered before scale-up. This allows the development of standards (defined and adjusted by DoE-derived data) that can apply to all stages of production and streamline validation and documentation.

QbD and PAT

The FDA has consistently required that companies must have:

- a detailed understanding of their manufacturing processes, including the parameters necessary for control
- defined the critical process parameters that are responsible for process variability that impacts product quality
- set up an appropriate monitoring and control system to ensure a robust process and consistent, compliant product

Therefore, it is no coincidence that these three requirements are the intersection of validation and PAT. PAT can properly be understood as simply a *quid pro quo* between the FDA and industry. The FDA is offering regulatory flexibility to industry in exchange for substantive proof of process understanding, analysis, and control allied with demonstrated product quality and compliance. The advantage is that they are offering to help smooth the regulatory approval pathway for innovations in process and analytical technology; a source of contention between industry and regulators for decades. PAT is lowering the regulatory approval bar that industry has been concerned was set too high for innovation.

The path forward for companies struggling with validation and confused about the application of PAT is threefold:

- First, develop an integrated validation plan.
- Second, select the appropriate statistical tools to conduct and analyze the results of multivariate experiments.
- Third, enhance the engineering systems that initiate, support, and maintain the validated state of processes and associated infrastructure.

This approach first and foremost provides for a complete understanding of the process and only then addresses the implementation of PAT.

Integrated Validation Plan

While validation execution would follow the industry standard V-Model shown in Figure 2, a fully integrated validation plan would include:

- a policy that includes a description of the company's philosophy and validation approach, including QbD and risk assessment/risk management (ICH Q8 & Q9)¹
- the master plan for validation (EU Annex 15)²
- site validation master plans (and specific project/product plans) that link all development, production, and quality control data that support the current facility, utilities, equipment, cleaning, control systems, methods, and processes for site products, including individual protocols and summaries
- validation standards (technical documents and a protocol template library) based on regulatory requirements and industry standards
- an organizational structure (Development, Engineering, Production, Quality, and Statistics) for the validation team, including roles, responsibilities, and handshakes

Figure 3 is also relevant, as it shows typical interrelationships within an integrated validation documentation hierarchy.

A validation program based on QbD provides the platform for PAT applications. Once the process is understood and the critical control points and critical process parameters have been defined, the determination can be made concerning PAT innovations.

How to Begin a PAT Assessment

1. Select a process step or unit operation.
2. Map that section of the process or operation, including the preceding and subsequent operations.
3. Conduct a risk assessment on the selected process or operation.
4. Collect and assess existing process or operation data – CPPs.
5. Determine additional data required for better process understanding – CPPs.

Only then would you be ready to make a PAT innovation assessment.

Regulatory Awareness

QbD-driven validation requires heightened awareness of and responsiveness to emerging regulatory trends and initiatives. The FDA's Pharmaceutical Quality Assessment System (PQAS), presented by Vibhakar Shah to the Agency's Advisory Committee Pharmaceutical Science (ACPS)³ in Oct 2005, is a case in point.

From a manufacturing perspective, PQAS poses the following questions:

- Appropriateness of process design?

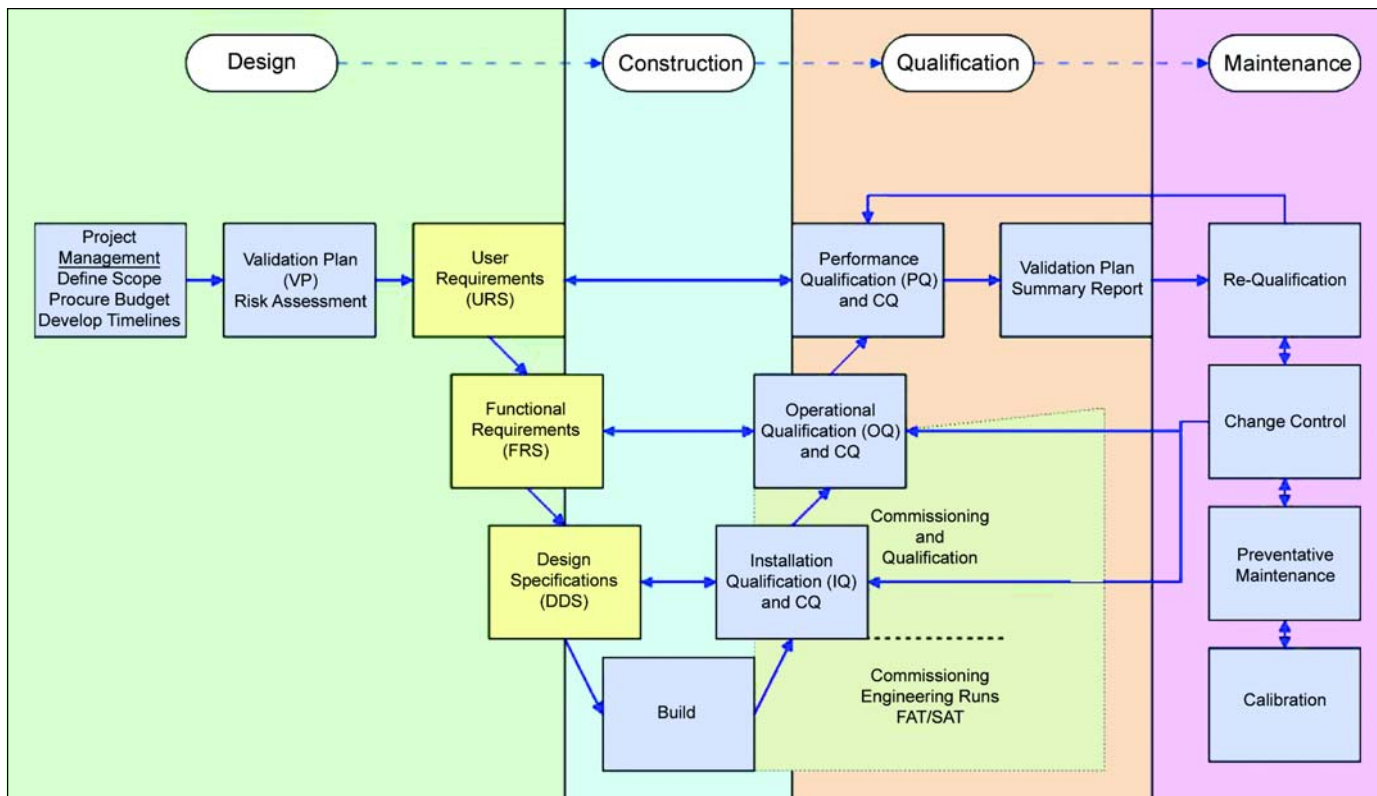


Figure 2. Process validation V-model.

- Appropriateness of in-process test acceptance criteria and CPP ranges?
- Adequacy of relevant environmental controls, e.g., for moisture or oxygen sensitive formulation?
- Suitability/capability of control strategy?
- Strategy for continuous improvement within the design space?

If we're not already doing so, we should start aligning our validation and ongoing metrics programs accordingly, regardless of our commitment to formal PAT. In Dr. Woodcock's efficient, agile, and flexible environment, the fact that corporate policies, plans, and procedures need to be recast ought to be viewed as an opportunity rather than a stumbling block. And in any case, the adoption of 21st century guidances need not automatically apply to legacy products and systems.

Real Time Release (RTR), which is a logical extension of Parametric Release and no more contentious, is another aspect of PQAS which should be factored into our process maps. Again based on the ACPS presentation, the 21st century technology transfer and validation efforts should be designed to take into account the following expectations:

- Ability to evaluate and ensure acceptable quality of in-process and/or final product based on process data, which includes valid combination of -
 - assessment of material attributes by direct and/or indirect process measurements
 - assessment of critical process parameters and their effect on in-process material attributes
 - process controls

- Combined process measurements and other test data generated during manufacturing can serve as the basis for RTR of the final product.
- Thus, demonstrate that each batch conforms to established quality attributes.

FDA's Aseptic Processing Guide (2004)⁴ is another topical example that challenges organizational response mechanisms. In this case, the guide is explicit in several areas, yet a time-lag exists in translating these requirements into succinct, testable criteria with key commitments often diluted or lost in the translation. The following two examples, taken directly from the guide, illustrate the point.

Airlock

A small room with interlocked doors is constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an aseptic processing airlock is to preclude ingress of particulate matter and microorganism contamination from a lesser controlled area.

From an architectural, HVAC, and metrology standpoint, there is enough here to be going on with in regard to risk-based compliance, and yet our system specifications/protocols are rarely so concise or focused.

Batch Monitoring and Control

Various in-process control parameters (e.g., container weight variation, fill weight, leakers, air pressure) provide information to monitor and facilitate ongoing process control. It is

essential to monitor the microbial air quality. Samples should be taken according to a comprehensive sampling plan that provides data representative of the entire filling operation. Continuous monitoring of particles can provide valuable data relative to the control of a blow-fill-seal operation.

Again, the standard response is crude and untraceable. Check your own monitoring and control process to see if it explicitly itemizes the following elements with associated instrumentation, units of measurement, and trend/archive frequencies predefined. If it does, you're top of the class.

- container weight
- container weight variation
- fill weight
- leakers
- air pressure
- microbial air quality

Summary

This section has presented ways to reform, not reinvent, the validation process, taking account of the FDA's plea for good science, expressed consistently since 1977. Economy and common sense should be inherent in the process, both of which confirm that validation should be embedded in workflows rather than treated as a just-too-late, after-the-fact activity. The validation response must be commensurate with risk; therefore, emphasis has been given to the process-understanding aspects of PAT, duly supported by statistical analysis and design of experiments, rather than the technology itself, sophisticated though it may be. Regarding the engineering/validation disconnect, the discussion has advocated the development of explicit QbD standards allied with mutual handshakes across the life cycle as the only logical solution to this contentious issue.

Section 2:

Engineering Statistics and Chemometrics

Introduction

This section describes how engineering statistics and chemometrics (the application of system theory and applied statistics to the large volumes of data collected in chemical processes) are currently viewed in pharmaceutical quality and manufacturing and recommends how they should be regarded. Applied engineering statistics is discussed as an essential tool that all quality and manufacturing staff should use routinely. The role of engineering statistics is described under the following headings:

- Organization
- Variability
- Specifications
- Statistical data analysis
- Control charts
- Sampling

Organization

Current State

Typically, statisticians in the pharmaceutical industry work and operate in three specialized areas within the discipline of statistics:

- Clinical-trial statisticians are the most numerous and support human trials.
- Pre-clinical statisticians support research and development, including animal trials.
- Physical science statisticians, including Certified Quality Engineers, Certified Reliability Engineers, Six Sigma Green Belts, Black Belts and Master Black Belts, and external consultants, are the smallest group. They support quality control, quality assurance, validation, manufacturing, pharmaceutical technology, process engineering, process improvement, and Process Analytical Technology (PAT).⁵

Most companies have few statisticians working in these areas so most projects and project teams do not benefit from their expertise. Although some colleges now provide courses in chemometrics, the majority of chemists and engineers have not taken courses in applied engineering statistics or chemometrics, and this training has not been required for professional chemists and engineers. The attitude is often 'if statistics were so important to success, my major professor would have required me to use it.' Those who take college statistics courses are often frustrated to find that the course is too theoretical and seems to have little practical application.⁶

Desired State

"Statistical thinking will one day be as necessary for efficient citizenship as the ability to read and write." H. G. Wells

In the desired state, the industry acknowledges the need for support specialists in engineering statistics and chemometrics, but also expects professionals to be familiar with basic applied statistics. Chemists and engineers should design and analyze their own data collection experiments

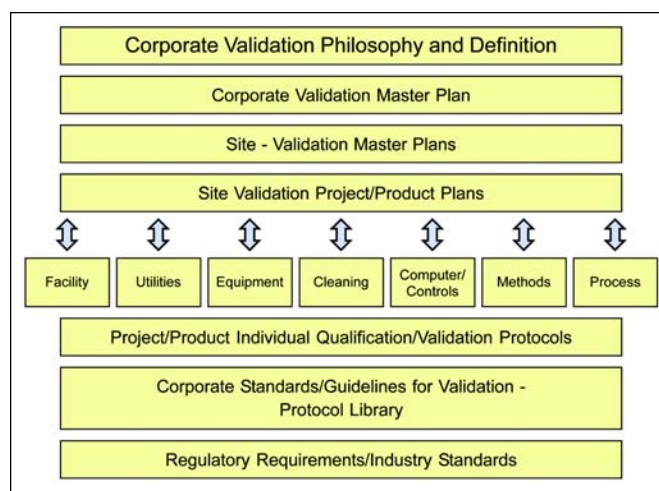


Figure 3. Validation documentation hierarchy.

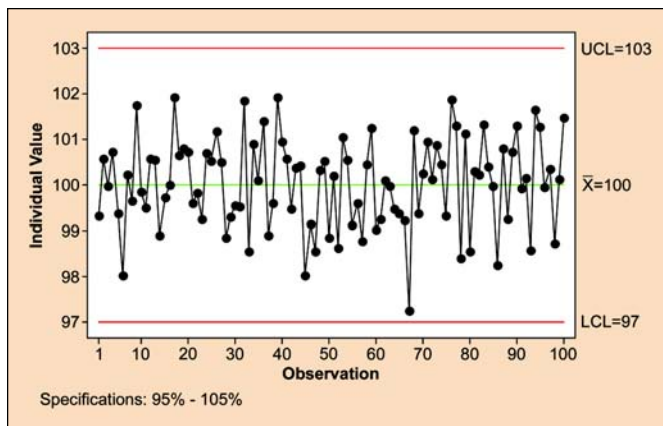


Figure 4. Control chart for individual values.

with a consulting statistician reviewing the draft protocols and draft reports.

Variability

Past State

In 1978, the Code of Federal Regulations (21CFR211.110(a)) had this important statement:

‘To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and drug product.’

Not many people read the above paragraph from the Good Manufacturing Practice (GMP) regulations and realize that the FDA was telling companies to reduce the variability of their manufacturing processes. Therefore, Ed Fry,⁷ while working at the FDA as Director, Division of Drug Quality Compliance, wrote this in 1985.

‘A set of specifications, limits, or ranges on desired characteristics is required. Then, the processes that cause that variability in those characteristics must be identified. Experiments are conducted (that is validation runs) to assure that factors that would cause variability are under control, and will result in an output that meets the specifications within the limits of the ranges that you had previously established.’

He continued,

‘What is it that has to be validated? Let me again cite what the GMP regulations say. The regulations require validation of those processes responsible for causing variabilities in characteristics of in-process materials or finished products. In some cases, it’s easy to identify what causes variability, but in other cases it may not be so easy. However, the regulations imply that not everything that takes place in a pharmaceutical manufactur-

ing plant causes variability. Therefore, some things don’t have to be validated. We never intended to require that everything [that] takes place in a manufacturing operation is subject to a validation study.’

It doesn’t get much clearer than that.

Current State

Variability is seldom considered an essential part of a validation study and when it is, it is considered ‘inherent’ in that nothing can be done about it. Unless the variability is wildly excessive, efforts are not made to reduce it.

Desired State

It is reasonable to assume that the 2004 PAT guidance was written to get companies back on track with the original intent of the 1978 GMPs, that is, one goal of validation being to reduce variation. The PAT guidance includes this statement.

‘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; and (3) product quality attributes can be accurately and reliably predicted over the design space ...’

Management should adopt the mantra, ‘where is the variability coming from and what specifically have you personally done today to eliminate it or reduce it?’

Specifications

For the discussion of specifications, too, it is useful to review the GMP regulations issued in 1978 before considering present and desired conditions.

Past State

In 1978, the Code of Federal Regulations (21CFR211.110(b)) stated, ‘Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.’

This seems clear enough. Use your past historical data and good engineering statistical practice to calculate the specification criteria.

Current State

How many current specification criteria have actually been determined using ‘previous acceptable process average and process variability estimates,’ (standard deviation) and ‘suitable statistical procedures?’ Yet, every day quality assurance accepts or rejects millions of dollars worth of material and product using specification criteria without supporting evidence and without verifying or justifying the validity of those criteria.

Desired State

Engineering professionals should use past historical data and good engineering statistical practice to calculate specification criteria. If historical data doesn't exist, use statistically designed experiments (DoE) to collect the data and determine the design and response space and from those the appropriate specification criteria.

Statistical Data Analysis

Current State

All too often, raw data is presented without even the most elementary analysis. Further, a short term view is fostered when historical data is not considered. Current data presented without reference to previous data in context is usually very misleading.

Desired State

Every engineering professional should have the basic statistical skills to present data in tables and graphs with appropriate summary numbers. Every presentation and report should tell a simple story in a compelling way.

Control Charts

Current State

The use of control charts seems to be spotty at best. While the GMPs refer to process control, there is no specific requirement that they be used. The regulation already quoted includes this:

'To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.' 21CFR211.110(a)

The term 'in-process controls' can, of course, mean many things to many people, but it is not a stretch to include statistical control charts as part of the definition.

Desired State

The desired state is given with clarity in the PAT guidance as follows.

'In a PAT environment, batch records should include scientific and procedural information indicative of high process quality and product conformance. For example, batch records could include a series of charts depicting acceptance ranges, confidence intervals, and distribution plots showing measurement results.'

Figure 4 is an example of a statistical control chart for individual values.

Sampling

Current State

Statistical sampling plans might be the weakest link in the chain of quality and manufacturing evaluation. Almost all companies use some form of statistical sampling plan to take

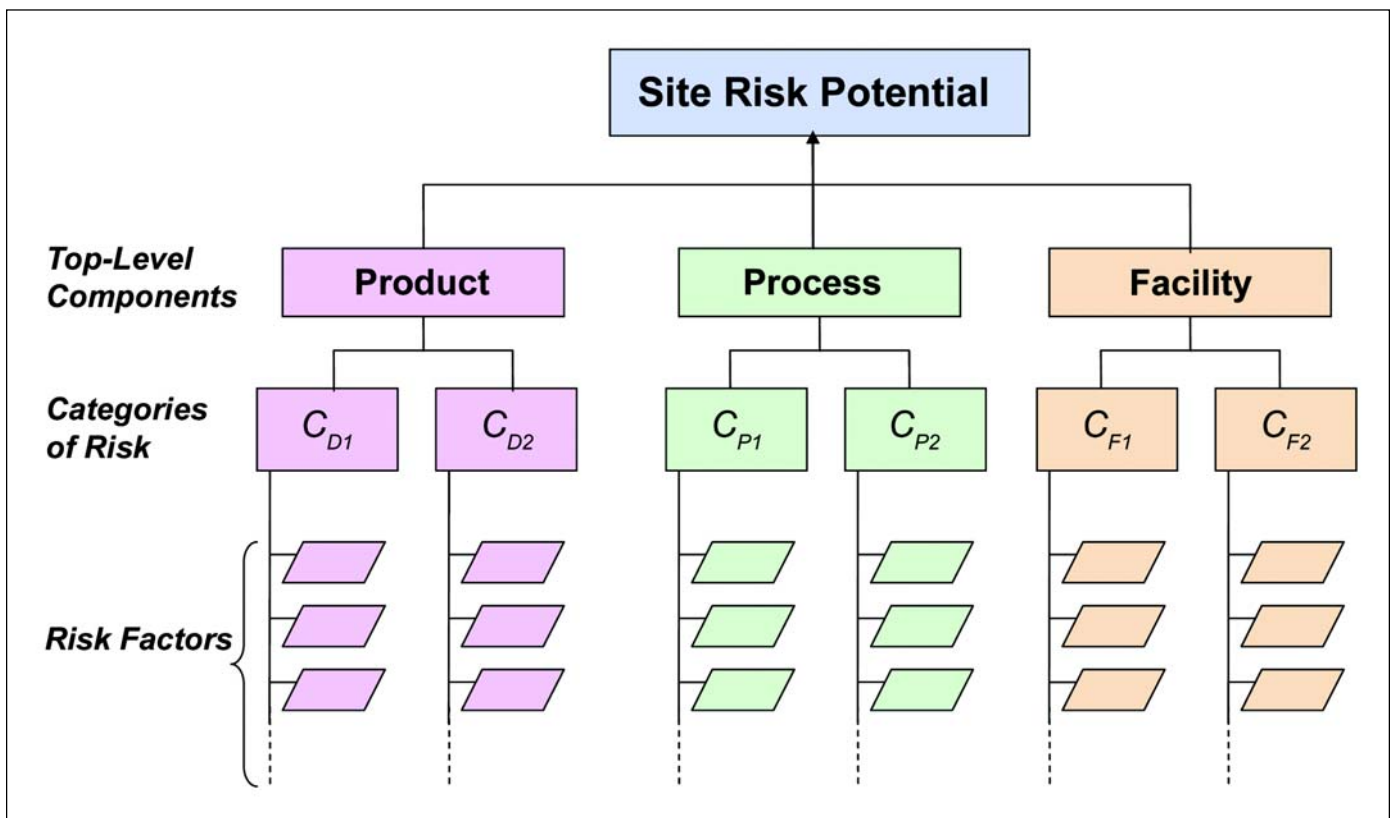


Figure 5. Conceptual organization of site selection model.

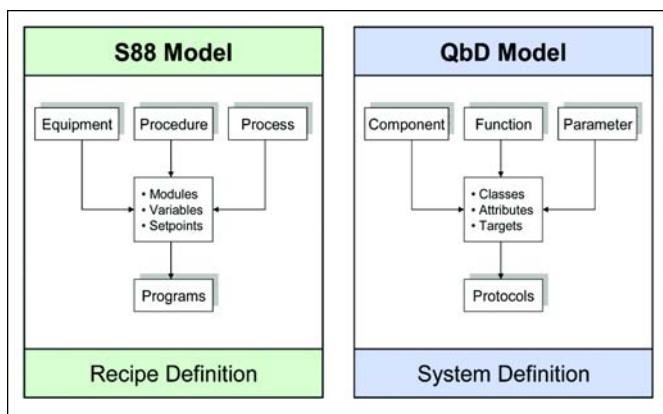


Figure 6. The S88 and QbD models.

samples for measurement. Most use ANSI/ASQ Z1.4⁸ for attributes. A very few use ANSI/ASQ Z1.9⁹ for variables. It also is rare that the company has actually trained the quality staff in the correct design, use, and understanding of these sampling plans. Yet, the quality department makes decisions worth millions of dollars based on plans that are designed incorrectly and samples that might or might not truly represent the lots being sampled. The GMPs require that samples be representative, but once the sample has been taken, it will never be known whether the sample is representative. Only by watching the sample being taken can it be verified that it is truly representative.

Desired State

The GMPs in 21CFR211.25 require that all personnel be trained in the 'particular operations that the employee performs...' Because employees use sampling plans and take samples, they and their supervisors must be trained in the correct use of the sampling plans employed. This includes some understanding of the statistical principles underlying the sampling plans.

Summary

This section has focused on engineering statistical areas and applications that are used or not used in the pharmaceutical industry for quality and manufacturing. Happily, the use of engineering statistics has increased in the last 10 years or so. However, this progress has been spotty. Only management can implement the desired state. Hopefully, the PAT guidance has created a new awareness that will stimulate companies into action and all companies will use engineering statistics and chemometrics designs¹⁰ to their own benefit and that of the ultimate consumer, the patient.

Section 3: Quality by Design (QbD) in Engineering Processes

Introduction

This section compares the current and desired states of pharmaceutical engineering, responding to Dr. Woodcock's admonition and addressing some of the observations in the previous discussions. The underlying premise is that histori-

cally, our manufacturing processes and procedures have been discontinuous and that our engineering practices have adopted an equivalent mindset, resulting in a number of self-inflicted and costly disconnects. By contrast, the desired state treats pharmaceutical engineering as continuous and self-evident, characteristics that will be developed and discussed under the following headings:

- Models
- Methods
- Materials
- Manpower

A basic example of applied QbD from an engineering point of view also is presented along with an MIT benchmark.

Models

Current State

Although our Good Automated Manufacturing Practices (GAMP)¹¹ colleagues have been instrumental in delivering the ubiquitous V-Model, there is no formal engineering model to speak of within the current state. Several attempts have been made to extend the basic V to accommodate validation in general - Figure 2, but what we really need is a scalable technical model that engineers can work with and remember.

By comparison, the FDA's *Risk-Based Method for Prioritizing cGMP Inspections*¹² (Sept 2004) contains a pilot model aimed at categorizing and assessing Site Risk Potential (SRP) as shown in Figure 5; the objective being to prioritize and schedule inspections and to eliminate subjectivity from the equation. This has direct engineering applicability, and can assist in the delivery of a Right First Time and sustainable asset base.

Desired State

The desired state calls for an ISPE-driven model that enables both existing and emerging pharmaceutical technology (including PAT) to be identified, categorized, and documented across the GEP/GMP life cycle. The model should be compatible with the current state initiatives mentioned above, and capable of handling major and minor projects alike with efficiency, agility and flexibility as prerequisites.

From an executable point of view, the *ISA-S88 Batch Systems Standard*¹³ offers a powerful prototype, geared toward the modular definition and execution of automated processes. Figure 6 shows the model alongside a proposed QbD counterpart. The similarities are striking: both exploit standard configurable elements; both assign set-points to variables as a function of risk; and both are self-documenting: programs being compiled in one case, protocols in the other. Most importantly, they are designed to be contemporaneous with minimum delay or interference between their input, processing, and output layers.

S88 has had a transformative impact on recipe definition and execution in our industry, and a properly developed QbD equivalent would have a similar effect on pharmaceutical engineering. Such a model would enable the traditional

system life cycle to be transformed into a genuine continuum, readily understood and accepted by engineers, end users, and regulators.

Note: For GAMP supporters, these vertical models insert a central class-laden spine into the vacant space of the traditional V, thereby connecting system requirements on the left to their associated protocols on the right with acceptance criteria being acquired *en route*.

Methods

Current State

Notwithstanding the wide range of design and scheduling tools that we consider commonplace, the current state engineering methodology is primarily manual and labor-intensive. Pharmaceutical engineers re-enter the same information into disconnected information systems many times in the course of their design, delivery, and validation efforts. This is a self-inflicted source of error and non-compliance, cumulatively accounting for an alarming percentage of our capital expenditures.

Piping and Instrumentation Diagrams (P&IDs) remain the dominant representation of the total system, in spite of their obvious physical bias. Specifications and associated equipment listings are copied and pasted as expedient throughout the life cycle, from risk assessment through project management, commissioning, and qualification. Maintenance and requalification are poorly served afterthoughts. Data exchange and analysis across applications is minimal, and change control is a tangled web. Quality Engineering standards do not exist to any real extent, and Validation doesn't trust us so they do it all over again. This results in a

proliferation of disorderly documentation, which, contrary to hearsay, adds no value and is of little interest to the 21st century regulator.

Desired State

The desired state methodology is based on an efficient, agile, and flexible execution of the model outlined in the previous section. The following discussion examines each of the model's three main layers.

Components, Functions, and Parameters

In the desired state, systems must be itemized with unique identifiers assigned to each component or element. The absence of explicit rules for tagging, within and across projects, remains the number one culprit in pharmaceutical engineering. Remember the maxim, 'no entities without identity;' and if you are playing the impact assessment game, be sure to include an appropriate qualifier (DI: Direct Impact, C: Critical, etc.).

When itemizing your systems, do not restrict yourself to physical assets only. Instead, follow S88's example and individuate your functions and parameters also; but do this in parallel rather than complicate or entangle your physical model. Such segmentation will be beneficial later on when you are attempting to generate specifications and protocols for different phases of your life cycle.

What is described here will be familiar to those engaged in Manufacturing Execution System (MES) implementations, where engineering and manufacturing Bills Of Material (eBOMs and mBOMs) are needed at different times for different reasons. The same applies within QbD, where

Key Points	Implementation
Product User Requirements are defined based on the process and its impact on the identified critical product attributes from the process knowledge report provided by development teams.	Level 1 Hierarchy: a. CQAs b. CPPs PRODUCT USER REQUIREMENTS
A series of risk assessments, evaluation and mitigation is performed during the early stage of design to ensure that process control and monitoring requirements, critical to control process variability, are designed into the system.	Level 2 Hierarchy (Level 1, plus...) a. Process Control Elements b. Monitoring Elements EARLY DESIGN
A design review and risk assessment is performed on the final design to identify the features, functions and components of the design that are critical to monitoring and control of product quality, along with their associated acceptance criteria.	Level 3 Hierarchy (Level 2, plus...) a. Features b. Functions c. Components FINAL DESIGN
The traditional IQ/OQ approach of quality control review of all technical verification of installation and operational verification is incorporated into the commissioning stage; with review of all technical testing, verifications performed and managed by the technical experts. On an exception basis, when 'critical to quality' elements can not meet their acceptance criteria, the quality unit is involved with the final review and follow up action plan.	Level 4 Hierarchy (Level 3, plus...) a. Tests b. Failures c. Actions COMMISSIONING
The Qualification approach leverages commissioning - modified to include pre-start up verifications (technical experts confirm that commissioning is completed and advise on any exceptions, GMP readiness such as SOPs approved and training) and a performance qualification (dry run, placebo or product) to confirm that the system effectively controls critical sources of process variation.	Level 5 Hierarchy (Level 4, plus...) a. Pre-start-up Verifications b. Performance Qualification QUALIFICATION
The standard includes a continuous improvement approach where post manufacturing performance is periodically evaluated to determine if the system continues to perform in a controlled manner or if improvements should be implemented to improve control.	Level 6 Hierarchy (Level 5, plus...) a. Evaluations b. Improvements CONTINUOUS IMPROVEMENT

Table A. ASTM draft guide for a science and risk-based approach to qualification.

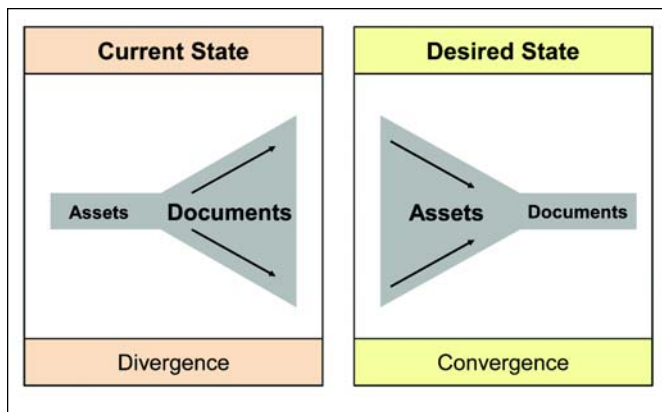


Figure 7. Funnel vision.

different representations of the systems and components at different stages (e.g., design, installation, operation, performance) are required.

Classes, Attributes, and Targets

By identifying your manufacturing subject matter, you can quickly establish a QbD class library, which in section 1 would include keywords such as *tank*, *pH meter*, *elution rate*, and in section 2, *control chart*, *experiment*, and so on. With such classes in place, follow FDA's SRP example and define quality attributes based on experience and input from your

Subject Matter Experts (SMEs). Be sure to define units of measurements for your quantitative attributes ($^{\circ}\text{C}$ or $^{\circ}\text{F}$, psig or barg, liters/min or gals/hr, dd/mm/yy or mm/dd/yy).

Along with your S88 and FDA associates, you are now in a position to classify your systems and components, and all that remains is to assign the relevant target values to the predefined attributes. This is pharmaceutical engineering at its leanest, the target values of your variables being what distinguishes one regulated technical element from another (these values also will determine your DQ agenda).

Note: As a pharmaceutical engineer, your mix of education and experience should mean that you are qualified to make these determinations - and to recognize when a particular class is deficient and needs to be modified or replaced.

Protocols

A protocol is an instruction set, and so is a computer program, whether it has been S88-derived or otherwise. In both cases, classes serve the additional role of self-assembling the requisite documented output. When you instruct your Recipe Management System to initiate a Temperature Control Sequence, it knows which script to invoke, for the simple reason that the sequence is an instance of a class which is unequivocally connected to the script. Furthermore, it executes the sequence routinely, predictably, and consistently. The same applies to GEP and GMP protocol generation within a QbD framework.

#	Work Item	Applied QbD
1	Register the required tank within your quality engineering framework	Tank acquires unique identity based on in-house rules, e.g. TK-106
2	Declare tank criticality based on ISPE impact assessment conventions (Direct/Indirect/No)	Criticality flag is appended to primary tag, e.g. TK-106 [D]
3	Categorize the tank based on your corporate or site class library	'Tank' class results in standard QbD attributes being assigned to TK-106A, e.g., working volume, internal finish, operating temperature
4	Render the TK template specific to TK-106 by defining the required target values for each attribute	Working Volume: 500 L Operating Temperature: 5.0 to 75.0 $^{\circ}\text{C}$
5	Embed roles and responsibilities as additional attributes, in line with the commitments made within your corporate/project VMP	IQ post-approval #1: Project Engineering OQ pre-approval #2: Process Engineering
6	Add required components to the TK-106 hierarchy, inclusive of criticality ranking	Each item acquires unique identity based on in-house rules, e.g., Agitator:A-106 [C], Temperature Transmitter: TT-106 [C]
7	Repeat steps 3 - 5 for each component in turn	TT-106: Transmitter Calibrated Range: -10 to +100 $^{\circ}\text{C}$ Recalibration Period: Monthly Owner: Metrology
8	Create parallel branches within the hierarchy corresponding to each major layer of the life cycle and assign the relevant components on an incremental basis	Design: URS-106; P&ID-106 Installation: A-106; TT-106 Operation: Mix; Transfer
9	Standardize the C&Q process for TK-106 and its components by utilizing test scripts written at the relevant class level	P&ID-106: DQ_Drawing TT-106: IQ_Transmitter Mix: OQ_Sequence
10	Auto-populate standard C&Q formats with data (i.e. tag no's, attributes, targets, scripts) extracted from your system model	P&ID-106: DQ_Drawing TT-106: IQ_Transmitter Mix: OQ_Sequence
11	Accelerate the above process for complex systems and projects by aligning your engineering spreadsheets with your class libraries	BLDG-100: 300 Rooms DCS-5: 2,500 I/O Process 6: 150 Samples Project 5: 500 Vendors
12	Query your model and transfer relevant subsets of data to and from Asset Management and other business systems	A-106 [Maintenance Query]: model no, vendor, spare parts list, warranty expiry date, lubricant, rpm min/max

Table B. Quality by Design in engineering processes.

There is a point here worth reiterating: within the desired state methodology, itemization and classification take primary position with validation treated as a consequential activity. This is the self-evident engineering which was referred to in the introduction, and as you can see in Figure 7 it delivers convergence rather than divergence.

There is another comparison between S88 and QbD which is important to note. Within S88, standard modules are rigorously qualified across their intended range (by vendors or end-users) before being put into active service. Individual deployments are then subject to verification rather than full-blown validation. There is no reason why this family-based approach cannot be applied to QbD with the same attendant benefits.

Materials

Current State

At input level, the current state uses material such as GMP regulations, ISPE/ICH guidances, and corporate policies/plans/procedures by the score. These are augmented by technical standards dealing with instrument calibration, piping design, and so on, although these items are rarely life science specific. From an output point of view, documents, drawings, and databases are generated in abundance, but with little regard to connectivity, continuity, or reusability.

Desired State

In the desired state, input material (i.e., regulations and user requirements) is translated into the relevant combination of classes, attributes, and procedures, and executed using the type of methodology previously outlined. Because emerging guidances get the same treatment, they can be rapidly deployed on behalf of the systems to which they apply. From a QbD point of view, ASTM’s *Standard Guide to a Science and Risk-Based Approach to Qualification of Biopharmaceutical and Pharmaceutical Manufacturing System*¹⁴ (2006, Draft Under Development) is a topical example as summarized in Table A. In order to identify material deliverables associated with such documents, just read between the lines. This results in essential tasks and milestones being identified with a view to formal execution via your chosen model and method.

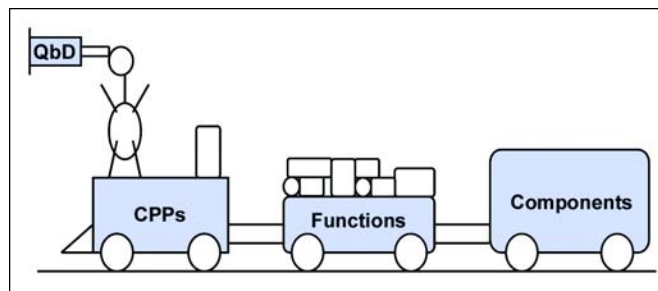


Figure 8. On track.

As with material inputs, QbD outputs should be equally informative and frugal. Resist the temptation to have as many formats and styles as there are days in the week, month, or year. A single format should be sufficient for system itemization, another for specification, and another for protocols, these documents being direct extensions of each other. Once again, the acid test is efficiency, agility, flexibility.

Note: For collateral evidence such as material certificates and user manuals, consider scanning and cross-referencing rather than putting up with the annoyance of managing and archiving hardcopy – often in triplicate or quadruplicate – for hardcopy’s sake.

Manpower

Current State

Currently, pharmaceutical engineering is organized as a series of independent specialties, each with its own skill-set, vocabulary, and methodology. Such specialties include process, mechanical, metrology, automation, and so on. Representatives from these departments ostensibly work together to deliver facilities and processes at optimal cost, quality, and schedule. The educational process encourages this drive to specialization, delivering engineers and technologists with specific rather than all-around capabilities.

Desired State

The desired state recognizes the need for specialization, but treats pharmaceutical engineering as a unified and integrated resource. In this scenario, engineers are multi-tasking with strong IT and analytical skills; ‘singular expertise being

1	Typical engineering design education focuses on specific aspects of design, such as the technical behavior of a set of elements interconnected in a certain way. By contrast, Engineering Systems focuses on a number of abstract concepts first, because they provide a general framework for guiding the development of many diverse kinds of systems, so that these systems will provide the desired functions in the desired ways.
2	Architectures may arise in the process of deliberate <i>de novo</i> design of a system; by evolution from previous designs with strong legacy constraints; <i>by obeying regulations, standards and protocols</i> ; by accretion of smaller systems with their own architectures; or by exploration of requirements via dialog between users and architects, to name a few known mechanisms.
3	Within the architecting process, several types of architectures are involved: <ul style="list-style-type: none"> • The functional architecture (list of activities or functions that we need to accomplish the system’s requirements) • The physical architecture (representation of physical components and their interconnections) • The technical architecture (elaboration of the physical architecture ... such that the system will achieve the requirements) • The dynamic operational architecture (a description of how the elements operate and interact over time while achieving their goals)
4	Systems are intended to have certain primary functions, plus other properties that we call ‘ilities’: durability, maintainability, adaptability, scalability, extensibility, flexibility and so on. The primary functions have immediate value while the ‘ilities’ tend to have life cycle value.
5	Complex phenomena become understandable only after their essential modules have been identified and characterized. A corollary requirement for understanding is that these modules act the same way in all combinations and that the types of interactions and interfaces can be enumerated and characterized.

Table C. The influence of architecting in engineering systems (MIT).¹⁶

no longer sufficient in our workforce'.¹⁵ Such all-arounders will be leading members of our 21st century project teams, delivering the efficiency, agility, and flexibility that both industry and regulator require - *Figure 8*.

To make this happen, manpower must facilitate dialog and data exchange across projects and disciplines. The establishment of a Data Dictionary Group has a major part to play here. The groups themselves need not be large, their mission being to develop and share standard semantics across applications, to define, implement, and identify opportunities for leveraging documentation and data within the QbD life cycle.

Table B illustrates the tank example from a quality engineering point of view, presented in tabular form.

The key point of the example is to emphasize the interconnected, incremental, and Right First Time characteristics of applied QbD.

Summary

In this section, the use of system architecting and modeling as prerequisites of Right First Time engineering is addressed. In particular, modularity and standardization is presented, arguing that complex pharmaceutical systems and processes are best specified, explained, and validated by reducing them to their essential elements and properties, based on logic rather than literature. Connectivity and concurrency is discussed, suggesting that critical components, functions, and parameters should coexist within a unified QbD framework and that these items should be self-documenting. Finally, it is imperative that 21st century pharmaceutical engineers are more self-assured, regulatory-aware, and frugal than their predecessors when conceptualizing and delivering facilities, systems, and processes of which they can be justifiably proud.

Conclusion

Dr. Janet Woodcock's urging that we become 'maximally efficient, agile, and flexible' has resonated with the three co-authors. Based on their collective experience, the authors' propose that QbD can achieve that state, while at the same time isolating and eliminating unwanted pseudo-validation from the workplace. Applying fundamental QbD principles to the design of process, data, and equipment systems delivers transparent and self-validating outputs sufficient to the needs of both industry and regulator. In this mode, validation is reinstated as a consequence of good science and good engineering rather than an isolated and expensive add-on as is too often the case currently.

In our conclusion, the keys to success are threefold:

- an integrated validation plan that provides a framework for defining and delivering compliant and robust manufacturing processes
- a statistical methodology to assess and reduce variability while identifying genuinely critical parameters and quality attributes and their associated ranges
- self-evident engineering and life cycle management techniques that deliver a Right First Time and sustainable asset base

All three must be highly modular and responsive to the challenges and opportunities that emerging regulations and industry guidelines present.

The intent of this article is to stimulate discussion and debate within ISPE, and subject to feedback, to conduct a follow-up workshop and establish a 'desired state' interest group.

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This article reviews the relationships between quality and regulatory practices, and the implications for business performers for suppliers of automated systems to the pharmaceutical manufacturing industry.

Regulatory Considerations and Business Implications for Automated System Suppliers

by Diarmuid P. Meagher, M. Saleem Hashmi, and William G. Tuohey

Introduction

In the last decade, pharmaceutical manufacturers have seen a proliferation in the international regulatory expectations with regard to automated systems used in manufacturing. These expectations have been accentuated by the emergence and application of the FDA's 21 CFR Part 11 and by the increased focus by regulatory authorities on the lifecycle activities surrounding computerized systems. Although ultimate responsibility for automated system compliance lies with the manufacturer, suppliers also are greatly affected by the requirements. This article will review the multifarious regulatory practices that have become part of the *modus operandi* of suppliers. Research into the relationships between selected regulatory practices and supplier business performance is presented.

Background

The regulation of the pharmaceutical industry has become increasingly rigorous and rigid over time due to a process labelled by some as 'regulatory creep' or 'regulatory spiral'.¹ Regulatory observations have been issued to manufacturers of drugs for such design related non-conformances as failure to adequately document software development, or failure to reliably manage changes to software. The FDA's Web site is filled with warning letters relating to computer system validation. While many of the deficiencies are related to manufacturer's responsibilities, some gaps cannot be closed without the involvement of the providers of the automated system in question. Hence, the regulatory reach is toward the supplier. The design, documentation, and control of automated systems must meet standards aimed at compli-

ance, almost from their conception. The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems has become almost a *de-facto* standard for management of lifecycle activities for suppliers.² The comprehensive scope of GAMP shows just how much supplier practices are affected by regulatory expectations. While many of the requirements can be fulfilled by adherence to good engineering practice and following software development standards such as the ISO series of publications, it would be difficult for developers to be successful in the pharmaceutical market without some working knowledge and experience of the minefield of the applicable regulations.

So What's a Supplier to Do?

There are many activities in which a supplier must be engaged in order to compete successfully in the pharmaceutical world. The provision and availability of design documentation is important to the manufacturer as the basis for understanding and controlling their systems and also to allow testing of those systems to be performed against fixed specifications. Increasingly, manufacturers involve developers in their validation process and can leverage factory testing of systems into their own validation packages in an overall effort to prove fitness for use. Supplier's assistance with the provision of the relevant validation documentation might then prove vital for customer relations. Certain design features of the systems themselves may be necessary for compliance. The FDA's 21 CFR Part 11 is an obvious example of where built in software features can be essential for compliance. Many systems cannot be fully validated unless the system itself

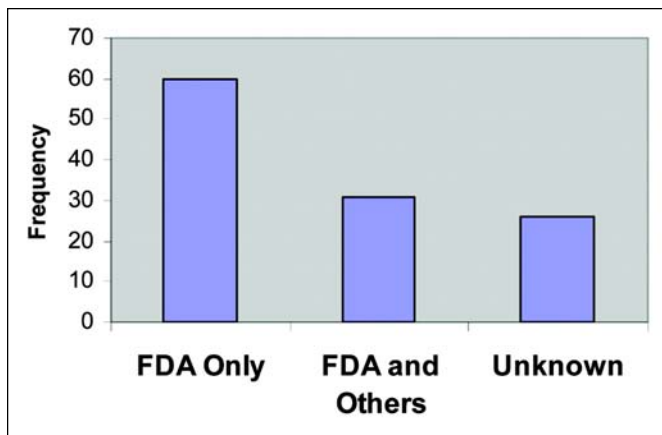


Figure 1. Distribution of respondents across regulatory categories.

allows the validation engineer to do so through appropriately designed interfaces and modules. Hence, regulatory compliance needs to be an early design consideration and developers need to be aware of, and trained in, the relevant Good Manufacturing Practice (GMP) regulations. Some software, such as embedded algorithms in subroutines, cannot be fully validated when the system is integrated. Therefore, it is imperative that such sub-systems are rigorously tested and that testing is documented before integration.

The quality management system operated by suppliers is subject to scrutiny by manufacturers during the selection process and periodically thereafter, and it might be wise for suppliers to have a quality system that has components that are geared toward regulatory requirements. The regulations themselves are subject to change and regular audits by the supplier of their quality systems and of their products to ensure that they continue to meet requirements could be advantageous. The use of the GAMP Guide by suppliers itself is a good indicator of commitment to compliance. Those providers who apply the principles of the Guide are highly likely to provide systems that meet many of the requirements for automated systems. Where the supplier's products have data processing capabilities, sound knowledge, and application of the rules for electronic records and signatures would be a fundamental requirement for business success in the pharmaceutical sector. From a manufacturer's point of view, important consideration must be given to the development strategy employed by the supplier and the mechanisms in place for control of code. In addition to this, the quality system environment itself must be in a fit state and effective to give maximum assurance to the quality of the automated system. Much has been written about the positive influences that quality management practices have on business success and will not be repeated here.³ However, what has not been determined is the relationship between specific practices aimed at regulatory compliance and business performance. This article presents a first attempt at research in this field.

Research Methodology

The research reported here was part of a broader project to establish the multivariate interactions between quality management practices, regulatory practices, and business perfor-

mance. In this article, only those elements pertinent to regulatory compliance are presented. A survey was conducted of 649 firms supplying automated systems to the pharmaceutical manufacturing sector worldwide. This sample was selected from industry databases and from advertiser indices from a series of prominent pharmaceutical trade and engineering journals.

Selection of Regulatory Variables

As no such research had been conducted before in this area, the selection of important regulatory practice variables to be measured in the survey was extracted from themes in the wider trade and academic literature. Several criteria emerged from the literature as being important for suppliers of automated systems in order to achieve compliance as summarized below:

- extent of knowledge of the GMP regulations, and the ability to apply them to the development and delivery of their products
- the extent of use of the GAMP Guide (although it is not suggested that compliance cannot be achieved without it)
- availability of design and validation documentation
- extent to which validation features are built into systems
- extent of knowledge and application of Part 11
- extent of source code availability to manufacturers
- extent of use of regulatory design reviews for software

These regulatory criteria were used as variables to evaluate the extent of regulatory practices by respondents.

Questionnaire Refinement

Once variables had been selected, questionnaire items were assigned to each regulatory practice variable. The questionnaire was extensively pre-tested and pilot tested before it was deemed complete. Pre-testing was done with the help of academic colleagues and a selected set of suppliers, which had shown a high level of interest in the study. Here, the pre-testers were asked to critique the questionnaire in terms of its simplicity, clarity, difficulty, ambiguity/specificity, burden, accessibility, relevance to study variables, and the feelings of the respondent regarding the completion of the business performance questions. The questionnaire was overhauled as a result of the pre-test. In particular, changes had to be made to the business performance questions. Here, subjective 'hard' measures of business performance were employed instead of objective hard financial measures. This meant that instead of being asked 'what was your percentage increase in sales last year?' Respondents were asked 'to what extent did last year's percentage in sales meet expectations?' There is much work in the literature to support the use of such subjective measures of business performance as reliable indicators of financial performance.^{5,6}

Pilot testing was performed by selecting 41 random suppliers who had previously agreed to participate in the study. Unaware that this was a pilot study, they were asked to complete and return the questionnaire. Twenty nine re-

sponses were received with no invalid questionnaires or negative comments regarding completion. The returned data was analyzed to ensure that statistical methods could be applied to it. As this was successful, no changes to the questionnaire were required, and the questionnaire was ready for the main administration.

Table A shows the relationship between the regulatory practice variables used in the study and the questions that were presented on the questionnaire to represent them.

Background Considerations

As well as questions relating to regulatory practice variables, a series of qualifying background questions were asked which requested information about:

- the regulatory environments suppliers were producing for
- the complexity of the automation in their products
- the criticality of the respondent's most critical products to the manufacturer's drug quality

Other questions regarding company size, age, and quality management practices also were asked. The regulatory environments that respondents operate in had to be determined in order to ascertain whether differences existed between respondents in differing environments, and whether generalizations could be made. The same applied to the complexity level of the software used in the respondent's product, and how critical that software was to the end user's drug quality. That is, more complex or critical software may lead to more stringent controls and practices by suppliers. As complexity of software is a difficult thing for respondents to categorize, the time taken to develop software was used as an indicator for measuring complexity, where low complexity software was that which took in the order of a few months to develop, and high complexity software took many months or even years to develop.

Survey Administration

The survey instrument was administered by electronic mail to each of the firms. The respondents could choose to use postal mail, a Web-hosted survey, or electronic mail return to respond. Each respondent in the sampling frame was individually invited by e-mail to participate, using a standardized e-mail text. Non-response was handled by a standard repeat mailing. Finally, 219 companies agreed to respond, although only 122 actually did, most citing internal resource pressures as the reason for non-response. 119 were valid. Where respondents failed to complete entire sections of the questionnaire, these questionnaires were considered invalid and were not used in the analysis. Typically for e-mail surveys, response rates of less than 10% are achieved;⁴ therefore, the 18.9% observed in this work compared very favorably. The high response rate may have been in part due to the familiarity by suppliers of completing quality/regulatory related questionnaires at the request of drug manufacturers.

Factor Analysis and Cronbach's Alpha

Factor Analysis involves reducing a group of indicators (questionnaire items in this case) to a much smaller group of indicators, or factors, to allow ease of analysis. It does this by finding underlying variance in the data common to a set of items, and grouping those items into a factor. In this case, when the set of 16 questionnaire items were subjected to factor analysis (Principal Components Analysis), three 'latent' factors resulted. Each factor was strongly correlated with a group of questionnaire items, and could be used to represent them. The actual questionnaire data for the group of questionnaire items represented by a particular question is summed together (this is called a summated scale) to give a factor value (i.e., a Direct Regulatory Involvement, Intrinsic Regulatory Compliance and Regulatory Documentation Availability score) for each questionnaire. A further test to ensure that all the questionnaire items linked to a factor actually vary together, and represent the same thing, is the internal reliability measure or 'Cronbach's alpha'. Here, a value of 0.7 or more shows that the summated scale is reliable. All factor derived scales in this study were found to be reliable as shown in Table B.

Data Analysis

The responses were collated and a series of statistical tools was used to reduce the data into manageable subgroups, which could be more readily analyzed. Factor analysis - Sidebar 1 was used to detect underlying latent factors in the data and to build scales from which meaningful interpretation of the data could be achieved. From the data in this survey, three regulatory practice factors emerged. The first factor represented those questionnaire items that represented direct involvement by suppliers in regulatory related activities. The second concerned intrinsic regulatory compliance, by virtue of the supplier's activities (Table B), and the third represented availability of regulatory related documentation.

Each factor extracted represents a unique feature of the data and the summated scores within each factor can be analyzed as a single variable. That is, all the questionnaire items comprising the direct regulatory involvement factor could be used to form a scale. In survey research, the reliability of scales is an important concern. A standard measure of internal consistency reliability (meaning that all items in a scale actually measure the same feature) is Cronbach's alpha. An observed alpha value of greater than 0.7 represents a reliable scale.⁷ For each of the regulatory practice scales in this research, Cronbach's alpha exceeded 0.7.

An identical process was followed to acquire data related to supplier business performance. Respondents were asked to state whether the following items had exceeded expectations:

Nonparametric analysis

Non-parametric techniques are useful for non-continuous data (that is, where 'gaps' appear between possible scores, such as with questionnaire answers where only five discrete levels can represent the answer), for where the distribution of scores is non-normal and for where there is a low number of respondents in a group. For the analysis in this work, Kruskal-Wallis H testing was used to detect significant differences across a number of categories (for example, was there a difference in regulatory scores across low, medium, and high complexity suppliers?). The Kruskal-Wallis test will not show which pairs within the groups cause the difference, it will just give an output that tells us that the three categories do not have the same mean scores in the population. Therefore, Mann-Whitney U tests were used to determine differences between pairs (was there a difference in scores between medium and high levels of complexity). This test is applied to each pair of categories and a 'significant' output shows that the mean scores for the pair of categories differ in the population. In this research, such techniques were used to ensure that assumptions of normality, continuous data, and number of respondents in a particular group were not required. This conservative approach leads to increased confidence in the findings.

- profit over five years
- sales over five years
- market share over five years
- current market share relative to competitors
- overall competitive position over five years
- new product sales over two years

A series of options were provided which could be used to determine whether expectations were exceeded, reached, or not reached. In all cases, the questions were directed to performance in the pharmaceutical market. After factor analysis, the data was reduced to two scales – one for profit and sales improvement against expectations and one for market share and competitiveness improvement against expectations. In each case, the Cronbach's alpha exceeded the 0.7 cut-off for internal consistency reliability. Table B shows the extracted factors and the corresponding scale items for both the business factors and the regulatory factors.

Thus, five new representative variables were created based on the summated scale scores for each factor.

Analysis and Findings

Statistical Methodology

Correlation and multiple-regression analysis were employed to determine the main relationships between the extracted variables. Non-parametric techniques (Sidebar 2) for hypotheses or 'difference' testing were then used to determine

whether background influences influenced scores for different respondent characteristics.

Background Data

In looking at the background data acquired through the questionnaires, it was important to establish that there was representation from across the range of possible suppliers 'types.'

First, it was important to establish the regulatory background profile of respondents. Sixty of the 119 respondents produced for FDA regulated environments only. Only two respondents developed systems for the European Medicines Evaluation Agency (EMA) market alone with 26 others developing for both the EMA and FDA markets (combined with some others such as the Pharmaceutical Inspection Cooperation (Convention)/Scheme markets, which include 27 European and Oceanic countries, and those who produced to International Conference on Harmonization guidelines). Only one respondent claimed that they developed their products within WHO guidelines for GMP and the WHO were not considered further in the study. The data was summarized into three groups to ease understanding and analysis as can be seen in the bar chart in Figure 1. Here the regulatory environment was divided into 'FDA only,' FDA and others, and 'Unknown.' Twenty six respondents reported that they did not know their regulatory environments. From this, it can be seen that those who produced for the EMA market generally produced for the FDA market, but the converse cannot be stated.

With regard to the complexity of automation (based on a seven point scale determined by development resource required), 8.5% of respondents had low complexity automation in their products, 39.5% had medium complexity, and 52% reported delivering high complexity products. Using a similar scaling system, it was revealed that almost 14% had solutions that offered low risk to the manufacturer's drug quality (low criticality), 42% had medium risk solutions, and 44% of respondents had products that were highly critical to the quality of the pharmaceutical product.

In terms of how long companies were in business, 61% had been providing solutions for the pharmaceutical market for

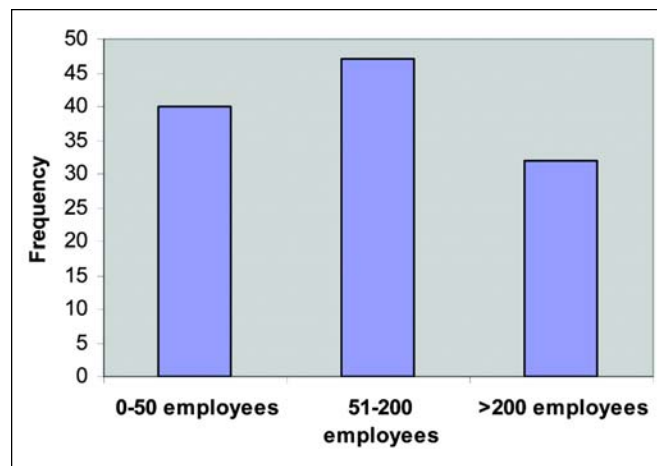


Figure 2. Distribution of respondent company sizes.

more than 16 years. The organization size distributions are shown in Figure 2. Here, it can be seen that there was adequate representation in the study from small, medium, and large companies and from those companies operating less than 16 years, and those operating 16 years or more in the pharmaceutical market.

In terms of statistical validity of the findings, it was important that each company in the population had an equal chance of selection. The use of standardized mailings assured this. Examining the respondent profiles in terms of regulatory environments, size, time in business, complexity of automation produced, and criticality of automated products, it can be seen that a good cross section of possible respondent profiles were represented, which gives support to the ‘external validity’ of the study. This means that generalizations to the entire population of automated solution suppliers can be made from the study, based on the 18.3% response rate (119 valid questionnaires out of a population of 649 suppliers).

Derivation of Relationships

Table C shows the correlation analysis between the regulatory variables and the business variables. Correlation analysis (Pearson’s *r*) was used to determine whether a change in regulatory practice scores is connected to a corresponding change in the business performance scores. As shown, there were statistically significant levels of correlation between some variables (statistical significance is imperative in order to be able to claim that the relationships were likely to exist in the entire population). Some were significant at the $p=0.01$ level (meaning that there is less than 1% chance that the correlation does not exist in the greater population) and others at the $p=0.05$ level. All other relationships were non-significant and hence, could not be generalized to the population.

From Table C, it can be seen that market share and competitiveness improvements have a low positive correlation with direct regulatory involvement, intrinsic regulatory compliance, and regulatory documentation availability. In addition, intrinsic regulatory compliance has a low positive correlation with sales and profit improvement. Changes in business performance are due to a variety of complex interrelated factors, but it would seem, that for suppliers of automated systems to the pharmaceutical market, that regulatory practices play a role. That is, from the correlations in Table C, it is clear that those companies who have better regulatory practices tend to have better business performance (above expectations). For example, a Pearson’s *r* value of 0.38 between ‘Intrinsic Regulatory Compliance’ and ‘Market Share and Competitiveness’ indicates that there is a moderate correlation between actual regulatory compliance, and a higher than expected market share and competitiveness improvement. Therefore, suppliers who are ‘better’ in regulatory practice terms are likely to exceed their own growth expectations. Figure 3 illustrates the correlation between Intrinsic Regulatory Compliance scores and Market Share and Competitiveness (above expectations) scores.

Questions	Related Variables
To what extent is there a) high knowledge of 21 CFR Part 11 b) training provided on 21 CFR Part 11 related matters? To what extent are products and systems <i>designed</i> to be compliant to standards for a) Electronic records b) Electronic signatures c) Electronic records and d) security?	Electronic Records / Electronic Signatures
To what extent a) are design activities documented b) is design documentation made available to manufacturers?	Provision of design documentation
To what extent is validation documentation made available to manufacturers?	Provision of validation documentation
To what extent is a) GAMP used b) GAMP used rather than other standards?	Use of the GAMP Guide
To what extent a) are features designed into products to aid validation b) is validation considered early in the design process?	Built in validation features
To what extent are regulatory design reviews carried out?	Regulatory Design Reviews
To what extent a) are system developers knowledgeable of the GMPs b) is GMP a major design consideration c) do system developers have regulatory training d) is the quality system focused on the GMPs?	Use of GMPs

Table A. Regulatory practices by suppliers and the associated survey questions.

Uncovering Unique and Important Contributors to Success

Correlation analysis does not tell the full story. That is, the relationship between one regulatory variable and a business performance variable may not be true for all values of the other regulatory variables or for all background variable values. In order to assess unique contribution by the regulatory variables, stepwise multiple-regression was used. When all the regulatory variables were entered into the model, the direct regulatory compliance variable was found to offer a unique contribution to market share and competitiveness. This resulted in regression equation 1 below:

Regression Equation 1

$$\text{Market Share and Competitiveness} = 1.620 + 0.353 \text{ Quality Related Factors} + 0.222 \text{ Direct Regulatory Involvement} + e_1$$

where e_1 is the error term.

This meant that the Direct Regulatory Involvement variable was the strongest and most representative regulatory contributor to market share and competitiveness, and that although the other variables were related to this variable, direct regulatory compliance was dominant. That doesn’t mean that the other regulatory variables were not important, in fact, they are all positively correlated to performance as shown in Table C. The R^2 value for a multiple regression equation tells us how much of the dependent (business) variable is caused by the independent components (regulatory, quality, and others) in the equation. Direct regulatory

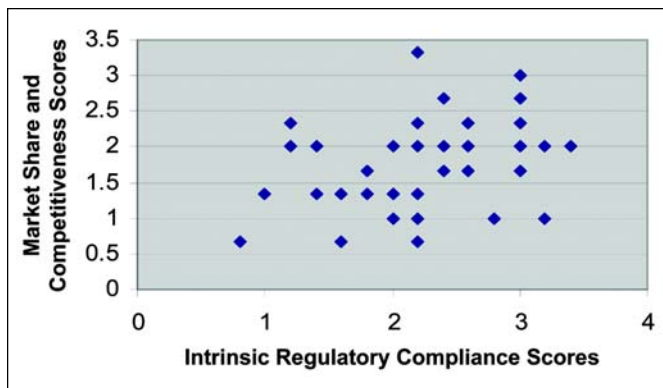


Figure 3. Correlation between Intrinsic Regulatory Compliance Scores and Market Share and Competitiveness Scores.

involvement added approximately 4% to the R² value for this regression equation; this means that 4% of the improvements in market share and competitiveness could be directly represented by direct regulatory involvement. Remember that this includes such practices as 21 CFR Part 11 competence, use of the GAMP Guide, and high awareness of the GMPs and their design implications. The total R² value for the equation was 20.1% and Regression Equation 1 was significant at the p=0.01 level (meaning that there is less than a one percent chance that it does not apply to the population as a whole.)

The research into quality practices (not reported here), and business performance in this sector showed that combining good quality practices and regulatory practices had substantial positive effects on business performance, as can be seen from the 20.1% R² value for Regression Equation 1. Quality practices were found to be significantly correlated with regulatory practices. The two sets of practices were found to be mutually beneficial, in that companies with high levels of quality practices also had high regulatory practice scores and vice versa. Therefore, while a 4% contribution to business performance from regulatory practice scores might not seem large, when combined with a sound quality system (high quality scores), the R² value for the regression equation was just over 20%. That is, by a combination of direct regulatory involvement activities and a good quality system, market share and competitiveness can be improved by 20% above company targets, which is a real business benefit and certainly worth the effort. It should be understood that as quality systems have been found to have been shaped by regulatory practices to some extent (as found in this research), then the overall contribution of regulatory practices to market share and competitiveness improvements can be seen to be substantial. That is, 4% of the improvement in performance is directly attributable to regulatory practices, and the remaining 16% contribution from quality practices is also partially due to regulatory practices influences.

When the regression model was applied to the sales and profit improvement situation, it was found that intrinsic regulatory compliance was the main player as shown in Regression Equation 2 below. Here it could be said from the R² value that 4.8% of improvements in profit and sales above expectations were due to activities focused on actual compli-

ance with the regulations such as building in validation features into products, and actual application of the GMPs to the quality system and to products.

Regression Equation 2

Sales and Profit Improvement =
 $1.520 + 0.237 \text{ Intrinsic Regulatory Compliance} + e_2$,
 where e₂ is the error term.

Background Consideration – The Role of Software Criticality as a Predictor of Business Performance Improvement

In order to establish that the regression relationships were not spurious, it was important to control for background factors also. To do this, all the background variables were plugged into the regression model, including complexity of automation and criticality of product to end user drug quality, length of time in business, and company size. It was found that for both the market share and competitiveness and the profit and sales models that the regulatory predictor in the equation was replaced by the criticality to end user drug quality variable. This means that criticality considered on its own could be used to represent the gamut of regulatory practices, and as a key driver for them. That is, the business performance of any given supplier to the pharmaceutical industry is related to the risk their products pose to the manufacturer's products or processes. Suppliers providing higher risk products tend to have higher market share and competitiveness and also profit and sales improvements than those providing lower risk products. This finding is possibly related to the stringent processes used by pharmaceutical manufacturers to select suppliers for their higher risk appli-

Direct Regulatory Involvement	Alpha
Electronic Records/Signatures System Developers Know GMP GAMP used GAMP used over other industry standards GMP major Design Consideration System Developers Regulatory Compliance Training	0.868
Intrinsic Regulatory Compliance	Alpha
Features Built In to aid Validation Validation Considered Early in Design QMS based on Regulatory Requirements Design is Documented Well Regulatory Compliance Audits	0.749
Regulatory Documentation Availability	Alpha
Design Docs made available Validation Docs made available	0.758
Market Share and Competitiveness against expectations	Alpha
Market Share Change over 5 years in pharma Market Share Relative to competitor change over 5 years Overall Competitive Position change over 5 years	0.755
Profit and Sales against expectations	Alpha
Profit Level change over 5 years in Pharma sector Sales Volume Change over 5 years in Pharma sector New Product Sales to Pharma over 2 years	0.755

Table B. Factors extracted from the survey data, the corresponding questionnaire items, and the reliability of the scale representing each factor.

cations. Also by their nature, specialist companies tend to be less in number than generalist companies, giving rise to an inherently greater market share.

Differences across Background Categories

Further analysis was performed to establish categorical differences in regulatory and business scores between suppliers who operated in differing regulatory climates, had differing levels of automation complexity in their products, and whose products had differing levels of criticality to drug quality. Various statistical techniques were used to establish whether significant differences existed in the data, including the Mann-Whitney U test for two unrelated data sets and the Kruskal-Wallis H test for several unrelated data sets. Only statistically significant differences (at the $p=0.05$ level or better) are reported here.

Looking at the regulatory variables, differences were found in terms of direct regulatory involvement. Differences were expected and found between those respondents who knew their regulatory environments and those who did not. Both the 'FDA only' and 'FDA and others' categories scored higher than for the 'unknown' category. If the respondent did not know their environment, it is unlikely that they would be adept at complying with the regulations. However, what was noticeable was that the FDA and others category scored significantly higher than for FDA only category. This suggested that an international view of the regulations was more likely to result in better application than a purely FDA focus. No significant differences were found between the categories in terms of intrinsic regulatory compliance. This can be explained by the strong relationships that the activities making up this variable have with general quality systems practices, which can vary from supplier to supplier regardless of regulatory environment.

The complexity of the software employed in respondent's products showed significant categorical differences with respect to both direct regulatory involvement and intrinsic regulatory compliance. The direct regulatory involvement variable showed an upward step change for each increase in complexity level from low to medium and from medium to high complexity. More complex systems are likely to be larger systems such as manufacturing control systems, manufacturing execution systems, quality documentation management systems, building management systems, SCADAs, distributed control systems, inventory management systems etc., which very often can have considerable impact on product quality. Therefore, to be competitive in the market, developers need to be in tune with the regulations. This is illustrated by GAMP which imposes requirements that increase in line with complexity and risk. In the case of intrinsic regulatory compliance, a difference in scores was detected between the low and medium complexity categories, but no difference was detected between the low and high, or medium and high categories so no useful pattern emerged. As an overall conclusion, from this study, it appears that companies operating with differing levels of complexity score differently in terms of regulatory practices.

	Market Share and Competitiveness	Sales and Profit Improvement
Direct Regulatory Involvement	0.31*	0.02
Intrinsic Regulatory Compliance	0.38*	0.24!
Regulatory Documentation Availability	0.22!	0.08
* Significant at the $p=0.01$ level		! Significant at the $p=0.05$ level

Table C. Correlation between summated scale scores for business and regulatory variables.

Differences in criticality levels resulted in significantly different scores for the regulatory variables and the two business factors. Hence, a marked difference in business performance scores was evident, contingent on the criticality of the respondent's product to drug quality. The step increase observed in direct regulatory involvement, intrinsic regulatory compliance, and availability of regulatory related documentation scores is probably attributable to the two-way relationship between manufacturers and their suppliers. In order to be effective in the market, developers must be prepared to meet customer's requirements in terms of compliance, and also manufacturers must demand levels of quality and regulatory practices from their suppliers commensurate with the risk to their processes. Many manufacturers will require the quality systems and related regulatory practices of their suppliers to be of a standard that matches the risk to the product or to their compliance effort, i.e., the GMP criticality of the automated system. Developers supplying the higher risk products did in fact have this greater regulatory emphasis and the corresponding knock on benefits in terms of business performance.

Summary

Adopting and enhancing regulatory practices for existing or prospective suppliers of automated products into the pharmaceutical market can have significant business advantages in terms of both market share and competitiveness growth, and profit and sales improvement, above expectations. That is, respondents who had better regulatory awareness and knowledge and who were more skilled at applying those regulations tended to report that their business performance in the pharmaceutical market was higher than their expectations. Although this general finding is true, it is not a case of one size fits all. The complexity of automation in the product and the risk the product poses from the drug manufacturer's perspective needs to be considered. Criticality plays a particularly important role in that companies that produced higher criticality products tended to have better regulatory practices, and enjoyed the corresponding knock on benefits in terms of business performance. However, high levels of regulatory awareness and application alone is not sufficient. There is a highly symbiotic relationship between general quality practices and regulatory related practices and both

should be linked and harnessed for maximum benefit. The level of quality and regulatory practices should be matched to the risk that their systems can pose to the manufacturer's drug quality and to the complexity of the automation used in their products. This ensures two things, the maximum benefit to product quality and drug users, and maximized business performance for the supplier.

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This article presents a study of cleaning performed to a clean coating pan in compliance with Health Canada's updated guidelines on cleaning validation.

Set-Up and Validation of a Clean-In-Place (CIP) System for a Coating Pan

by Stefania Ucci, Alessandro Spadoni, Caterina Funaro, Guia Bertuzzi, Roberto Trebbi, Giovanni Ciaramella, Paolo Colombo, and Ruggero Bettini

Introduction

The accurate cleaning of manufacturing equipment and facilities has always been a mandatory requirement for the pharmaceutical industry. Today, it is becoming more and more stringent because of many different reasons, including the introduction of more potent active pharmaceutical ingredients, as well as the need to comply with increasingly demanding regulatory guidelines. In this respect, the validation of cleaning procedures is a crucial activity to avoid cross-contamination, not only for manufacturing sites, but also for the sampling-filling suite in research and development.¹ This activity im-

plies the assessment of the efficiency of the cleaning steps for eliminating ingredients and detergent residues.

Equipment contamination stems from the materials used in the production, as well as from the environment and the people.² In order to reduce manual intervention, many industries are developing manufacturing machines equipped with Clean-In-Place (CIP) features.

In this study the clean-in-place of a coating pan was studied as a paramount example of difficult to clean pharmaceutical equipment. In particular, the compliance of the CIP procedure with the most updated guidelines was verified.³

The study was carried out by performing both direct (swabs method) and indirect sampling (rinse solutions) methods.³ The swab direct method is the FDA recommended technique because it is a direct measurement and guarantees a precise assessment of the cleaning efficacy.

Direct sampling offers the advantage of evaluating the level of contamination per given surface area; however, indirect sampling, although difficult to access surfaces and systems that cannot be routinely disassembled,⁴ can be checked.

Set-Up of CIP System

In general, a coating pan can be cleaned either manually or automatically (CIP), depending on company investment. When manual cleaning is adopted, the cleaning procedure must be standardized to assure reproducibility.



Figure 1. 300 liters maximum capacity coating pan.

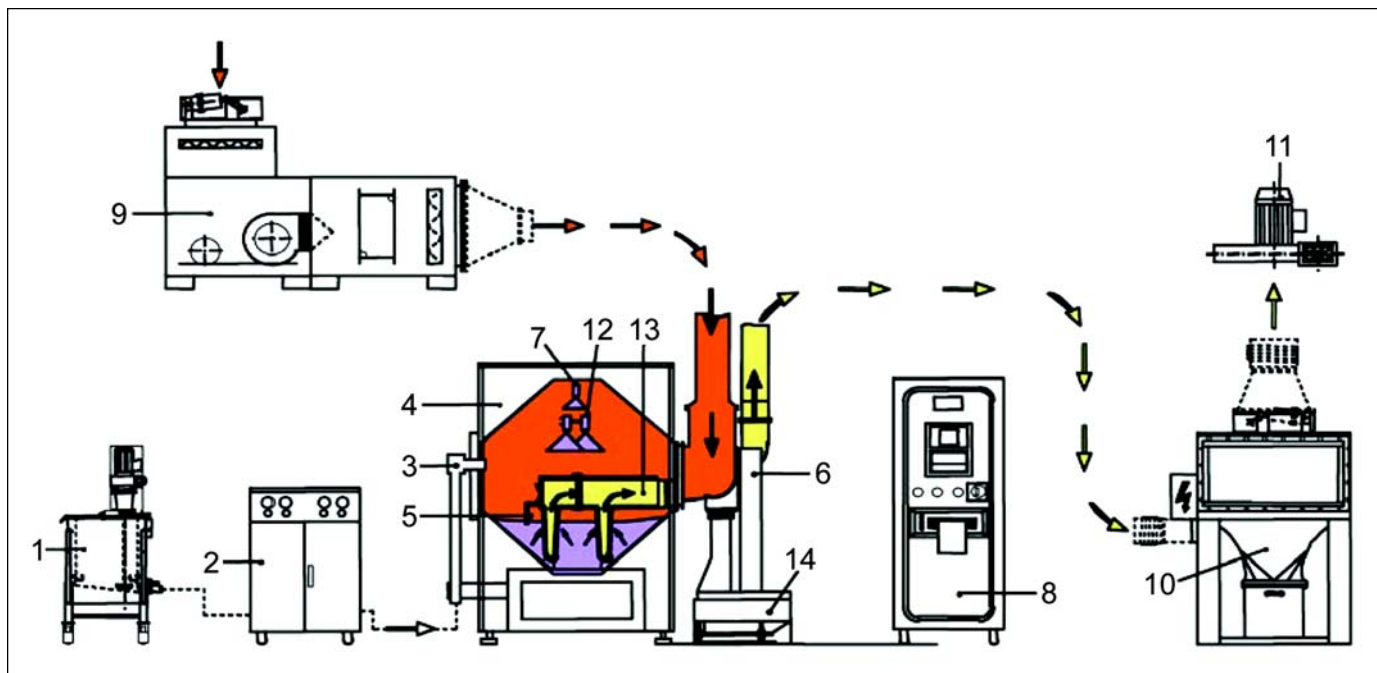


Figure 2. Schematic representation of the system arrangement: 1-product tank; 2-dosing unit; 3-sliding guns; 4-coating pan; 5-temperature probe; 6-in and out air device; 7-sugar spray guns; 8-control panel; 9-air treatment unit; 10-dust collector; 11-out air fan; 12-film spray guns; 13-drying paddles system; 14-paddles sliding system.

The aim of the CIP is:

- reduction of the cleaning time
- optimization of the use of detergent and water
- total or partial elimination of manual intervention.

The last point is of particular importance because it implies the reduction of the operator exposition to potentially harmful compounds.

Usually, when passing from manual cleaning to CIP a reduction of 50% of total cleaning time can be observed.

With a CIP system, the amount of water and detergent, used is optimized because the cleaning device, e.g., spray nozzles, spray balls, sprays the cleaning fluid in each direction, covering the total pan surface without waste.

A modern CIP system would enable saving money in terms of higher plant utilization and also of detergent (i.e., by recycling cleaning solutions), water (i.e., the system should be designed to use the optimum quantity of water), and man-hours saving.

Finally, CIP process times can be reduced without the addition of circulation pumps, valve manifolds, large tanks, and other equipment requiring a substantial initial investment and repeating maintenance costs.

With respect to other studied cases,^{5,6} the set-up of a CIP system for a coating pan is a more challenging issue to be addressed since the film forming materials nebulized firmly stack not only on the dosage form, but also on the machine's surfaces; in particular, the cleaning process involves critical areas such as spraying gun arms and irregular or difficult to reach surfaces.

Usually, for evaluating the efficacy of a cleaning process, a marker substance is used. This substance should be removed efficiently and there should not be significant quantity³ inside the machine or in the following batches of product. During the cleaning process, detergent, that can be either acidic or alkaline in nature, is used.

Using an acidic detergent, basic substances can be dissolved and easily removed, while the dissolution and elimination of acidic products is more critical. A successful cleaning process in this last situation (acid substance, acid detergent) would be indicative of a good possibility that the cleaning-in-place process could be successfully applied to many other substances. For this reason, in the present work, the coating pan was washed with an acidic detergent and the sodium salt of fluorescein was used as marker.

In particular, the validation was performed using the following scheme:

Cleaning Step

- production of a first batch of tablets coated with a film forming solution containing materials partly soluble in water and fluorescein sodium as a water soluble marker;
- cleaning phase through cycles of pre-washing, washing with acidic detergent, and rinsing;
- analysis of pre-washing, washing and rinsing water;
- visual inspection and metallic surfaces swabbing;
- analysis of rinsing waters to quantify phosphates and total organic substances (TOC) content.

Contamination Step

After the cleaning of the pan, the coating of a second tablet batch was performed using a coating mixture having a composition similar to that previously mentioned, but without marker to check for possible tracer cross-contamination.

Recovery Step

The discharged water after the cleaning process was analyzed to check whether the added marker could be totally recovered with the cleaning procedure.

Materials and Methods

Cleaning Trial

The trial was performed on a 300 liters maximum capacity coating pan - *Figure 1*. *Figure 2* reports a schematic representation of the system arrangement.

All operations performed during the validation of the CIP system were described in detail in Standard Operation Procedures to guide the operators in correctly performing all the different steps.

The CIP system used is managed by electro-pneumatic controls that enable washing cycle by means of spraying lances *Figure 3* inside the pan in AISI 316. Lances are installed on a wheeled device complete with closing disc for the pan front door. Each lance is equipped with spray nozzles, positioning micro switch, and quick coupling double-shutting valve.

Washing nozzles are fixed inside the equipment to achieve cleaning up to the outlet air duct of the rear ventilation unit. During each cleaning cycle, the machine automatically stops the pan in the proper position to discharge the washing fluids from the discharge valve. The system includes the hydraulic/pneumatic pre-fitted on separate skid and allows the use of two different washing liquids, one line emptying by means of compressed air.

The circuit is formed by butterfly valves in AISI 316 (DIN 1.4401) with pneumatic actuator; one-way valves; stainless steel pipes with Tri-clamp 1"; 1/2" connections; flexible hoses in Teflon® coated with AISI 304 (DIN 1.4301) stainless steel-mesh for the connection to the washing nozzles; pilot motor for automatic and manual pan speed adjustment; stainless steel/brass discharge valve welded to the pan cup with stainless steel return spring and seal; stainless steel tank and rubber water piping hose; tank raising pneumatic piston with position control micro switch; pull box with terminal bard; electromagnetic brake unit to stop the pan in the discharge position; and one inductive sensor for pan stop and speed control.

The CIP system allows for the cleaning of the inner parts of the coating pan, while the parts outside, in particular supply and exhaust air ductwork, are cleaned separately.

Tablets of lactose spray dried 60%, microcrystalline cellulose 39%, magnesium stearate 1% used for the coating processes, both with and without fluorescein Na, were prepared with a tablet press operating at the maximum speed of 360,000 tablets per hour.

For the production of a batch of tablets, coated with a taste-masking film, the pan was loaded with 100 kg of the tablets. Adapted aspirating paddles for reduced batches were used to exhaust the air from the core's bed.

A film coating solution, containing 1.66 kg of hydroxypropylmethylcellulose (HPMC), 0.166 kg of polyethylene glycol (PEG) 6000, 0.166 kg of sodium fluorescein,



Figure 3. Detail of the lance with spraying nozzles during a typical washing step.

0.0738 kg of sodium bicarbonate, and 18.16 kg of water was sprayed by means of 4 guns (nozzle diameter 1.4 mm and AIR CAP n°1). The coating time was one hour and the final weight gain 2%. The adopted operating parameters are reported in *Table A*.

At the end of the coating process, the tablets were unloaded. To unload the tablets, the discharge device was connected in the pan that was rotated for a few minutes at the minimum speed.

The line was cleaned spraying 8-10 L of hot water at the maximum speed. The reservoir and the drying paddles were cleaned separately with hot water and dried.

Before pan cleaning, the guns were re-mounted in the pan and the CIP performed. During each cycle, the cleaning steps were the following: paddles support cleaning; pan cleaning; front and rear door cleaning; pan rolling; discharge.

Parameter	Minimum Value	Maximum Value
Inlet Air Temperature (°C)	65	75
Core Temperature (°C)	40	43
Inlet Air Rate (m³/h)	800	900
Pan Negative Pressure (mmca)	-1.5	-2
Atomization Pressure (bar)	2.5	3
Spray Rate (mL/min)	100	200
Pan Speed (rpm)	3	9
Gun Distance (mm)	240	250

Table A. Process parameters for the taste masking coating.

The final phase of the CIP provided drying by blowing hot air inside the pan.

The washing cycle developed through the following phases:

Pre-Washing

This phase removed most of the residual material from the machine surfaces. In this phase flow 315 liters of hot (60°C) tap water (pH 7.6), at 6 bar and pressure 35 L/min were used.

Washing

318 liters of detergent solution (0.97% w/v) in hot tap water at 6 bar pressure and with a 35 L/min flow were employed for

Sampled Surfaces	Area (cm ²)	Fluorescein Na (µg/cm ²)
Glass front door surface	1513.9	1.2 × 10 ⁻³
Inflatable seals surface in contact with front door window	255.7	6.0 × 10 ⁻²
Front door surface in contact with inflatable seals + front door surface in contact with pan	751.6	1.2
Front door internal surface	1227.1	5.5 × 10 ⁻⁴
Spraying guns arm (up to support) + flange surface	1079.9	7.6 × 10 ⁻⁴
Support surface + cap surface + cylindrical surface	607.8	2.1 × 10 ⁻³
Gun surface + aircap (x 4 guns)	1095.2	3.8 × 10 ⁻²
Coating product tube + atomization air tube (extraflex) + compressed air tube	452.4	1.0
Ring blocking the frontal surface	940.4	1.8 × 10 ⁻³
Pan internal surface left side	400	3.8 × 10 ⁻⁴
Pan internal surface right side	400	3.4 × 10 ⁻⁴
Pan internal surface upper side	400	1.8 × 10 ⁻⁴
Pan internal surface between mixing baffles	400	1.1 × 10 ⁻³
Pan surface between mixing baffles near and above the discharge valve	400	5.5 × 10 ⁻⁴
Mixing baffles surface (left side of the discharge valve)	1556.8	7.9 × 10 ⁻⁴
Mixing baffles surface (right side of the discharge valve)	1556.8	4.9 × 10 ⁻⁴
Cylindrical surface of right washing lance	824.0	5.1 × 10 ⁻⁴
Cylindrical surface of left washing lance	824.0	2.5 × 10 ⁻³
Pan internal surface lower side	400	3.9 × 10 ⁻⁴
Pan internal surface upper side	400	2.5 × 10 ⁻⁴
Glass lamp surface	63.6	1.1 × 10 ⁻³
Frontal surface of drying paddles system	652.2	5.8 × 10 ⁻⁴
Inclined surface of drying paddles system	561.2	1.0 × 10 ⁻⁴
Lower vertical surface of drying paddles system	163.4	6.0 × 10 ⁻⁴
Upper vertical surface of drying paddles system	852.4	2.3 × 10 ⁻⁴
Cylindrical surface of the external ring of the drying paddles system	594.9	3.1 × 10 ⁻²
Inclined surface of the drying paddles system	529.6	4.6 × 10 ⁻⁴
Ring frontal surface	949.4	1.5 × 10 ⁻⁴
Tube surface of drying paddles system	4027.3	1.5 × 10 ⁻¹
Back surface of drying paddles system	663.6	2.1 × 10 ⁻³
Paddles support (total surface)	394.8	4.4 × 10 ⁻³
Cores temperature probe surface	377.2	6.2 × 10 ⁻³
Internal surface of inlet air tube	200.0	3.1 × 10 ⁻³
Outlet air tube	1403.9	3.1 × 10 ⁻²

Table B. Surfaces of the pan sampled and quantity of fluorescein Na per sampled unit surface after the CIP procedure.

removing all soluble and insoluble materials. The detergent contains phosphoric acid, thus allowing for the check of the efficacy of the rinsing phase through the analysis of phosphates with the "Phosphates limit essay" according to European Pharmacopoeia IV 2002.

Rinsing

This phase was divided into two steps and completely removed the detergent. In the first step, 320 liters of demineralized water pumped at 6 bar pressure were used; during the second step, in turn divided into two cycles, 287 liters of demineralized water for each cycle of water were used.

Drying

During this final phase, the pan, rotating at 20 rpm, was dried with hot air (temperature 100°C, absolute humidity 5.8 g/kg), for 30 minutes with a flow of 2500 m³/h.

Sample Collection

To assess the efficacy of the cleaning procedure, three samples of the liquid discharged at the end of each phase were collected. After the drying phase, the washed surfaces were visually inspected under UV light (253 nm).

Analytical Procedures

All samples were analyzed for pH and for fluorescein Na content. Samples obtained from the rinsing step also were analyzed for phosphate and total organic content. Before analysis, every solution was diluted with a buffer solution at pH 8 (Ph. Eur. IV) in order to assure complete fluorescein Na dissolution and filtered through a 0.45 µm membrane.

Fluorescein Na concentration was determined spectrophotometrically in buffer solution at pH 8 (Ph. Eur. IV) at wavelength of 493 nm. Samples whose concentration was below the limit of quantification of the spectrophotometric method were analyzed spectrofluorimetrically with absorption at 493 nm and emission at 515 nm (limit of quantification as low as 0.001 ppm).

As previously stated, the phosphates determination was performed according to the European Pharmacopoeia IV 2002 "Phosphates Limit Essay." A 100 mL of the sample solution was added with 4 mL of sulphomolybdic reagent, shaken, and added with 0.1 mL of stannous chloride solution. The standard was prepared in the same manner using 2 mL of phosphate standard solution (5 ppm phosphate) and 98 mL of water. The color of 20 mL of each solution was compared after 10 minutes. The color of any test solution should not be more intense than that of the standard.

Besides the visual comparison with the reference standard as described in European Pharmacopoeia, the absorbance of the sample solution was measured spectrophotometrically at 340 nm.

The determination of the Total Organic Carbon (TOC) was performed according to USP 28.

Swab sampling was performed using a hydrophilic cotton swab of 24 cm² soaked in 1 mL of a NaHCO₃ (0.5% w/v) solution. Table B lists the parts of the machine sampled along

Sample	Absorbance (340 nm)	Phosphate Concentration (ppm)
Reference Ph. Eur. IV	0.3828	0.1
2nd Discharging Phase	0.3336	< 0.1
2nd Rinsing Phase	0.2996	< 0.1
2nd Dripping Phase	0.3083	< 0.1
3rd Discharging Phase	0.3336	< 0.1
3rd Rinsing Phase	0.3159	< 0.1
3rd Dripping Phase	0.3101	< 0.1

Table C. Phosphate concentration in rinsing water.

Furthermore, it would have to be demonstrated that at the end of the rinsing phase, the characteristics of the discharged water would be identical to those of used water.

The visual check with ambient and UV light (253 nm) did not expose visible residues, except some minor spots on the upper part of the gun surface. Table A reports the amount of fluorescein Na found in different parts of the machine per unit of swabbed surface. It can be observed that in all cases, the amount recovered was very low and well below the specific limit required from the adopted guideline.

The cleaning procedure also was evaluated by monitoring the concentration of the marker in the discharged water. The fluorescein Na concentration in the pre-washing, washing, and rinsing water is presented in Figure 4 and 5 for spectrophotometrical and spectrofluorimetric analysis respectively.

It can be observed that the fluorescein Na concentration dropped below 1 ppm after the sixth step of the pre-washing phase - Figure 4.

In the rinsing phase (Figure 5), a general trend toward a progressive diminution of the fluorescein concentration in each sub-phase could be evidenced. At the end of this phase, the tracer concentration leveled around 0.01 ppm.

To further evaluate the characteristics of the water discharged during and at the end of washing operation, the pH value, phosphates concentration (indicating the residual detergent), and TOC were evaluated.

As illustrated in Figure 6, the pH of the discharged water went down during the washing procedures because of the presence of acid detergent, thus returned very close to the value of the demineralized water.^{6,8}

Phosphates concentration is presented in Table C. The values obtained for all samples were under European Pharmacopoeia IV limit (0.1 ppm), indicating that the rinsing procedure was able to eliminate completely detergent residues.

Table D lists the TOC concentration in rinsing waters. All values of TOC are higher than the Pharmacopoeial value of TOC for deputed water (500 ppb) and of the demineralized water used (242 ppb) although a trend toward a progressive reduction of TOC value can be clearly evidenced.

To assess whether after pan cleaning tablets production can be contaminated, three batches of tablets were produced and their fluorescein Na content measured. Table E reports the quantities and the concentration of fluorescein Na found in these placebo tablets. The concentration found was around 0.4 ppm independently to the pan sampling position. This

value is 20 times lower than that established by the adopted specifications as maximum acceptable limit (10 ppm).

Finally, the total amount of fluorescein Na recovered from pre-washing, washing, and rinsing waters was 39.399 g, which represents 98.5 % of the theoretical quantity introduced into the pan in the recovery trial.

Conclusion

In general, the cleaning of a coating pan represents a difficult task, as many issues should be considered in order to obtain a satisfactory result. In particular, the main problem that should be addressed is related to the difficulty of removing from the pan surface composite, cohesive materials, often containing water insoluble components.

In the present cleaning validation trial, we selected a tracer practically insoluble in acidic solutions and we used an acidic detergent in order to test the worst-case scenario.

From the results obtained, we can conclude that with the adopted procedure, the tracer substance almost could be completely eliminated after the first step of the cleaning procedure and after the washing procedure no residual was left inside the pan.

The water discharged after the CIP procedure had characteristics comparable to those of the supplied water in terms of pH and phosphate content. However, TOC values indicated a minimal, but still detectable organic contamination.

The results of the placebo trial indicate lack of cross-contamination between subsequent productions.

The recovery trial clearly showed the quantitative elimination of the tracer from the pan.

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Phase	TOC (ppb)
2nd Discharging Phase	1360
2nd Rinsing Phase	974
2nd Dripping Phase	1840
3rd Discharging Phase	1160
3rd Dripping Phase	832

Table D. Carbon concentration in rinsing water.

Sampling Position	Fluorescein Na, µg (s.d.)	Fluorescein Na Concentration (ppm)
Back Pan	0.114 (0.008)	0.46
Front Pan	0.104 (0.014)	0.41
Center Pan	0.101 (0.008)	0.39

Table E. Amount and concentration of fluorescein Na per tablet.

4. FDA, *Guide to Inspections Validation of Cleaning Processes*, 1993.
5. Nicoli, S., et al., "Validation of a Clean-In-Place System on a Capsule Filling Machine," *Pharmaceutical Technology Europe*, 15 (10) 2003, pp. 27-35.
6. Bonfanti, A., et al., "Clean-In-Place System Evaluation of a Rotary Tableting Machine," *Pharmaceutical Technology Europe*, 9 (4) 1997, pp. 31-38.

About the Authors



Ruggero Bettini graduated in pharmacy in 1991 at the University of Parma. In 1994, he received a PhD in pharmaceutical chemistry and technology at the same University. From 1994 to 1997, he was a Postdoctoral Fellow in the Department of Pharmacy, University of Parma. From 1997 to 2002, he held the position of Assistant Professor at the School of

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Dr. Munro discusses the state of quality and compliance today, relating his experiences gained from high-level roles in industry and regulation. He shares his thoughts on major industry challenges ahead, including generics, biotechnology, the relationship between the regulator and the regulated, and harmonization.

Editor's Note: The views expressed in this interview by Dr. Munro are his own and should not be attributed to his current or former employers.

PHARMACEUTICAL ENGINEERING Interviews

Gordon Munro, PhD, Senior Vice President, Quality Assurance, Watson Pharmaceuticals



Dr. Gordon Munro has a BSc in pharmacy and a Master's and Doctorate in analytical chemistry. He is a Fellow of the Royal Pharmaceutical Society (UK) and a Chartered Chemist.

He was initially employed within the pharmaceutical industry by Glaxo more than 25 years at various times in research, production, and quality assurance of both drug substances and drug products.

His career incorporated a range of senior technical positions working in the UK, Singapore, and the US, as well as several years in Glaxo's International Quality Assurance Division. His final role was as Director of Quality and Compliance for Glaxo Wellcome Operations, responsible for all quality assurance and health, safety, and environmental matters.

For seven years, he was Director of Inspection and Enforcement Division for the United Kingdom Medicines Control Agency, where his responsibilities included the GXP Inspectorate; the licensing of manufacturers and wholesale dealers enforcement of Medicines Legislation; provision of laboratory services to the Agency; and the British Pharmacopoeia.

He represented the Agency on the PIC/S Committee of Experts, the EMEA Ad Hoc Inspection Working Group and European Regulators at ICH on Q7A - Good Manufacturing Practice for Active Pharmaceutical Ingredients (as rapporteur), and Q9A - Quality Risk Management. During his period with the Agency, he was acting Chief Executive for a year and a half.

He joined Watson Pharmaceuticals, Inc. in June 2004 as Senior Vice President of Quality Assurance, where he is responsible for all quality programs, and ensuring a coordinated and integrated approach to quality at all of Watson's facilities. He recently joined the ICH Q10 Expert Working Group as an IGPA observer, is a member of the ISPE International Leadership Forum, and Chair of ISPE's Regulatory Affairs Committee and the IFPAT Manufacturers Association (IFPAT^{MA}).

Q What is your educational background?

A I have a degree in pharmacy with pharmaceutical chemistry and a Master's and Doctorate in analytical chemistry.

Q What led you into a career in the pharmaceutical industry?

A While working toward my degree at Strathclyde University, I particularly enjoyed the medicinal chemistry part of the course and coming into contact with members of staff who had spent time in the industry so I decided that was where I would like to start my career.

Q What experiences and training best prepared you for your current position?

A The combination of training in pharmacy with analytical chemistry and the experience of development, manufacturing, and quality assurance gained over the years, allied with living and working in different countries and cultures, best prepared me for my current position.

Q Could you describe your quality philosophy?

A I believe that it is essential to provide patients with medicines of consistent, reproducible quality that meet their needs, and this requires good people working as a team in a systematic, disciplined, and cost effective manner. To achieve this means striving to improve and to be more than merely in control or competent, but to be “clever” in building quality into products and sustaining this throughout their lifecycle through continuous improvement.

Q What do you see as your primary responsibilities and major challenges in your current position?

A The primary responsibilities in my current role are to oversee the development and execution of all quality programs at Watson and ensure coordinated and integrated approaches at all of our A facilities. The major challenges I see include making sure we continue to adapt successfully in the rapidly changing world of generics, while maintaining consistent quality and ensuring that we are cost competitive. In particular, this includes making sure that we respond to the changing regulatory environment.

Q What are the major challenges faced by a senior quality executive in a pharmaceutical organization?

A I think the challenges are very similar to those faced by senior staff in most organizations. This includes providing effective leadership; ensuring that there are enough high caliber, well motivated, empowered people; making sure the organization stays current with changes that are taking place in the environment in which we operate; and if possible, helping to shape that. However, factors which present additional challenges more specific to a senior role in a pharmaceutical organization are the intensity and comprehensiveness of the industry-specific regulatory requirements and the high profile which medicines have with the media, public, and politicians.

Q How do these differ from a large global company such as GSK compared to your current company Watson Pharmaceuticals?

A In my experience, there are not many differences at the high level in the challenges although there are differences between brand and generic businesses which impact on how the challenges are approached. One such difference is the scale of operations. In a large research-based company, typically one tends to be involved with a relatively small range of products with larger volume per product, whereas in a generic company, one tends to work with a broader product portfolio and smaller volume of each product, creating the need to be more flexible, while still maintaining the consistency and quality of operations and products. There is also a greater emphasis on speed in the generic industry during development and pre-submission activities, because of the significance of being first to file. Another example is that as cost competitiveness is a given, customer service assumes a greater importance as a differentiator between any company and its competitors.

Q What are some of the key metrics used in your organization to measure business, quality, and production performance or success?

A We use a variety of metrics, most of which are in common use in the industry. For example, we use earnings per share, cash flow, right the first time, cost of goods, cycle times, turnover rates, customer service levels, and compliance metrics, such as percentage of deviations per batch, numbers of recalls, field alerts, observations received, or other indicators of status of inspections. Recently, we have been aligning quality objectives with the Quality System Model developed by the FDA and working with some composite, risk-based metrics which are proving to be interesting.

Q What has been your most fulfilling role so far in your career?

A I've been very fortunate in having an ongoing series of fulfilling

roles and being able to move on from one to another at points in time when my personal satisfaction level dropped. Consequently, I wouldn't like to differentiate which has been the most fulfilling particularly as the personal satisfaction has come from different aspects of each job. However, all my roles have been in the pharmaceutical arena which, in itself, has always provided me with an overarching sense of being involved in something very worthwhile.

Q What have been the significant changes in the industry in the past decade and what are the challenges for the future?

A I think that the most significant changes for me have been the ongoing consolidation of the industry, the shifting of more and more of the manufacturing base to lower cost countries, the increasing impact of biotechnology and focus on vaccines, the negative change in the press, the general public and governments' perceptions of the industry and its regulators, and the increased demand for transparency and provision of information on both business activities and products. Another major change has been the greater emphasis on cost and cost benefit being driven by the larger purchasers of medicines and particularly governments. For the future, I believe that the major challenges will be in managing newer technologies dealing with the impact of such developments as nanotechnology, novel delivery systems, and personalized medicine, while maintaining cost levels that individuals and healthcare providers can afford. The increasing trend toward providing more medications directly to patients will further emphasize the need for better, clearer communication. There is also the basic need to ensure a good supply of medicines at a bearable cost in developing countries while sustaining the necessary funding for future research and development. However, I think the greatest challenge faced by both the industry and its regulators is communicating clearly without causing undue concern to an increasingly risk averse audience that (while there is no absolute guar-

antee for every individual) the benefit of taking medicines (as directed, for indications for which they have been approved by the regulators) greatly outweighs the risks involved. Meeting all or most of the challenges I have mentioned also should support re-emphasizing the value of the industry in healthcare and reducing the current focus on cost.

Q What are your views on managing a regulatory agency? What did you find successful – what worked, what doesn't work, and how did your training or career influence your management style? How does it differ from pharmaceutical industry management?

A In my view, managing a regulatory agency requires the same basic management skills and approaches that prove successful in the private sector. However, there are different challenges in how to deploy them given the more bureaucratic systems and lower levels of empowerment allied with greater rigidity and more hierarchal structures typical in government organizations. For example, when I first joined the Agency, I experienced a lot of frustration in getting things done, as decision making and change seemed to take much longer than anticipated. In matters of policy, this is appropriate because in a regulatory agency, they generally have a wider reaching impact than in industry, but there should be no need for delay on lesser more tactical issues. The absence of some of the discretionary benefits such as meaningful bonuses and share options which are common in the industry means there are fewer meaningful ways to motivate through variable rewards related to performance of teams or individuals. So, recognition, training, personal development, and ensuring job satisfaction become even more important than in the private sector. I find it difficult to generalize on what works and what doesn't work. In all management situations, I think this varies from individual to individual and team-to-team rather than organization to organization although an organization's culture is a major factor

in what works and what does not. In government, the culture is more conservative and risk averse which contributes to the slower decision making and rate of change, which is in surprising contrast to the shorter term perspective taken of budgeting and "business" strategy.

Q Your career has encompassed wide global quality responsibilities and also a senior role with a European regulatory agency – What do you believe can enhance the working relationship between the pharmaceutical industry and the regulators?

A In my experience, the vast majority of people in the industry and regulatory bodies are trying to achieve a common goal of safe, effective medicines being made available as quickly and consistently as possible to those who need them. However, I think that due to the events of recent years (for example, in the area of safety), there is a lower level of trust between the regulator and the regulated and improving this would enhance working relationships. To help ensure this trust, there needs to be more open exchanges of views and positive listening by all involved. In this context, I think it is very useful that there are organizations such as ISPE where regulators, industry, and academics can come together in a relatively informal environment and discuss matters of common interest. I also think that it's very useful if there is interchange of staff between regulatory agencies and the industry, and particularly for regulators to recruit a proportion of key staff with industrial experience, because in my opinion, to regulate effectively, it is essential to understand the industry which is being regulated. Such a level of understanding, I believe, strongly facilitates communication and a development of mutual understanding and trust between the regulated and regulator. In addition, given the internationalization of the industry, greater communication between and within regulatory bodies, coupled with the harmonization of requirements and their interpretation, would be very useful.

Q What are some of the major current GMP inspection issues of non-compliance?

A Sadly, in my experience of monitoring such issues, particularly while working for the Agency, during which time we published a number of papers relating to this topic, the common issues in GMP deficiencies remained pretty constant from year to year. Such inspectional observations included batch release by the Qualified Person (in Europe), quality system deficiencies, documentation errors, design and maintenance of premises, cleaning validation, potential for microbial contamination and non-microbial contamination; I have no doubt they will continue to be among the major recurring issues.

Q You were much involved as a regulator in the ICH arena particularly with Q7A for APIs – How do you envision the initiatives with international harmonization will develop in the next few years and how much of a continuing role will ICH have in this process?

A I expect in the short term that ICH Q10, the Guideline for Pharmaceutical Quality Systems, will be completed in 2007. Q8 (Pharmaceutical Development) may be supplemented to define guidance for individual dosage forms and so with Q9 (Quality Risk Management) and Q10, provide a more detailed framework for a more structured risk-, science- and systems-based approach to ensuring product quality throughout the lifecycle of the product. After that, I think the most fruitful areas within Quality/Compliance for ICH may well be to look at the regulatory aspects of some of the developing trends in the science of medicines, manufacture, and control, such as personalized medicines, miniaturized processing, and other areas of new technology where there will need to be some adaptation of the current approach to understanding and controlling processes and product quality. Such areas should be easier to negotiate if they are developed in advance of individual members of the interna-

tional community having established their own guidelines so that all parties come to the discussions with open minds. Overall, I hope that the harmonization process will survive. It can be tedious and time consuming but I believe there is enormous benefit to regulators, industry, and most of all, patients, in having harmonized standards helping to ensure consistency of products and through reducing duplication, reducing cost. Furthermore, as compliance in my view will have to continue to be primarily voluntary, (given that no regulator will ever have enough resources to check all operations one hundred percent of the time), the benefit of having standards, which are mutually acceptable to both the regulator and regulated, whenever possible, plays a major part in ensuring the willing cooperation by the majority of those to whom they apply.

Q Can you briefly describe the function and responsibilities of PIC/S? Global membership by regulators is increasing and do you think the organization can be the catalyst for continuing harmonization of GMP standards and systems worldwide?

A PIC/S started out as the Pharmaceutical Inspection Convention, an inter-government, treaty-based organization within the European Free Trade Association (EFTA). This has subsequently developed into the Pharmaceutical Inspection Cooperation Scheme which is a more global organization of regulatory authorities currently focusing primarily on good manufacturing practices and quality systems for inspectorates. Much of the focus is on mutual cooperation and exchange of knowledge, information, and experience. In this context, it is a less formal forum than for example, other equivalent meetings such as the Committees in Europe for GMP and inspections. As such, I believe it has been and should continue to be an excellent catalyst and vehicle for harmonization of GMP standards, systems, and their interpretation worldwide. The news that the FDA has applied to become a mem-

ber is very interesting and potentially should strengthen the organization, significantly increasing its ability and credibility as an agent for the harmonization and development of GMP standards and their implementation.

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

A I am currently a member of the International Leadership Forum and in 2006 became the Chairman of the Regulatory Affairs Committee, a role which regrettably I have not made enough time to discharge to my satisfaction. I initially encountered ISPE not long after it was founded, but my first real contact came through colleagues when GAMP was taken under ISPE's umbrella which I think was in the early 1990s.

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 I believe that ISPE is an extremely powerful forum for the exchange of views, knowledge, and information between individuals, companies, regulators, academics, and between and within each of these constituents. This is particularly true as it is a non-political, non-lobbying organization encompassing a very broad range of individuals and companies from around the globe with a vast wealth of knowledge relating to research, development, manufacture, and regulation of pharmaceuticals.

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 Over the next five years, I'm not sure that we will see truly major breakthroughs, perhaps more a continuation of the ever accelerating broadening of knowledge and change. I do

think we'll continue to see progress in the understanding and control of manufacturing processes, in their automation, possibly their miniaturization, and adjustments to meet the challenges of personalized medicines. In addition, I think the industry in general needs to pay more attention to the clarity of the information which it provides, which may lead to significant developments in the way the information is presented, formatted, and delivered. Furthermore, with the apparently increasing threat of counterfeiting and the recent detection of such products in the legitimate supply chain in America and Western Europe, I think more attention will be paid to means of preventing or making counterfeiting more difficult using both overt and covert means and enhanced control of the supply chain including "track and trace" approaches.

Q What is your opinion of re-importation of drugs to the US or other countries? What impact do you think re-importation will have on your business – if any?

A I believe that if re-importation is properly controlled, in principle, it should not present a threat to patients. However, there are additional difficulties in controlling the re-importation supply chain to maintain product integrity during the process of moving product across national borders. At the moment, I do not believe that re-importation plays a major role in the generics arena as cost differentials tend to be somewhat lower than they are for brand products. I believe that illegal supply over the Internet poses a much greater threat and challenge than re-importation per se.

Q What kind of activities do you enjoy in your free time?

A What free time? Seriously, I very much enjoy spending time with my wife, family, and friends. I enjoy traveling, sports of all sorts, although mainly a spectator now, reading, music, wine, and generally keeping fit. 

This article presents an overview of the comparative risks between the pharmaceutical industry and other industries, placing the hazards of pharmaceutical products in a context of overall public safety.

Practical Risk Management

by David Stokes

Introduction

The life sciences industry is undeniably moving toward a risk-based approach to managing quality and regulatory compliance. However, risk management can appear complicated and impractical, may fail to contain costs, and may even fail to mitigate important organizational risks.

Before embarking on any project involving risk management, participants should understand some of the practical principles that are not explained in many of the industry standards and guidelines.

This is useful for anyone who is:

- starting a process to define or revise their organization's approach to risk management
- conducting risk management as part of a current project
- managing risks as part of their day-to-day activities

This article will present risk management, including risk management terminology, ISO 14971, and the ICH Q9 risk management processes. A discussion of the differences between risk analysis and risk evaluation will be presented, arguing that in many cases, a relative assessment of risk is a more pragmatic approach than a qualitative or quantitative assessment. An example will illustrate how different categories of risk can be assessed in a comparable manner across the entire pharmaceutical enterprise. Referencing the GAMP® Risk Assessment model, an approach to the risk assessment of large, complex computer systems, highlighting the need to clearly distinguish between risk impact, risk likelihood, and probability of detection will be summarized.

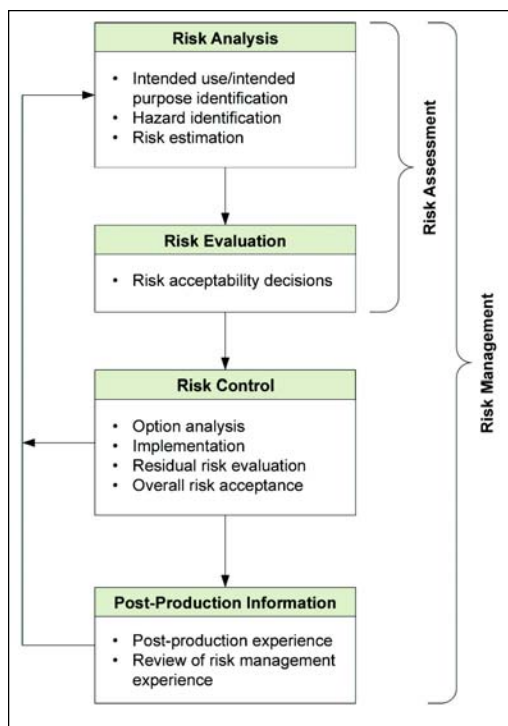
Terminology

Fundamental to practical risk management is a working understanding of the terminology that is used. Different sectors use different terminology, usually derived from different standards or guidelines. As an example, in the medical devices sector, the ISO 14971¹ standard uses specific terminology and professionals in this sector often talk about 'hazards analysis' rather than risk assessment; however, as can be seen in Figure 1, this standard uses many terms that are consistent with other risk management processes.

Practical risk assessment is easier when consistent terminology is used by all groups and departments in the organization. This may be difficult to achieve given that some groups will have their own terminology. An example of this may be the manufacturing of bulk Active Pharmaceutical Ingredients (APIs), where process engineers may be required to conduct safety (and/or chemical) Hazard Operability Analysis.

As a minimum, it is useful to provide a cross-walk between the different terms and definitions used. This allows different groups within an organization to follow mutually understood

Figure 1. Schematic representation of ISO 14971 risk management process.



Term	Definition
Hazard	The potential source of harm.
Risk Assessment	Systematic process of organizing information to support a risk decision to be made within a risk management process.
Risk Identification	Systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.
Risk Analysis	The estimation of risk associated with the identified hazards.
Risk Evaluation	Compares the estimated risk against given risk criteria using a qualitative or quantitative scale to determine the significance of risk.
Risk Control	Actions of implementing risk management decisions
Risk Reduction	Actions taken to lessen the probability of occurrence of harm and the severity of that harm
Risk Acceptance	Decision to accept risk
Risk Communication	Exchange or sharing of information about risk and risk management between the decision maker and other stakeholders
Risk Review	Step in the risk management process for taking account of new knowledge and experience

Table A. Terms and definitions from ICH Consensus Guideline Q9 “Quality Risk Management.”

approaches to risk management.

For the sake of consistency, this article will use terms defined in the International Conference on Harmonization (ICH) Consensus Guideline Q9 “Quality Risk Management.”²

Most of the terms in the ICH Q9 Guideline are derived from other international standards, but ICH Q9 is solely intended to apply the principles of risk management to Quality Management and is non-proscriptive with regard to the methods that can be used to assess, analyze, and evaluate risks. As covered in ICH Q9, a discussion of formal methods of *Risk Assessment* such as Hazard Analysis and Critical Control Points (HACCP), Failure Mode, Effects, and Criticality Analysis (FMEA), and Fault Tree Analysis is outside the scope of this article.

One approach used within the pharmaceutical computer systems validation community is the risk assessment approach described in Appendix M3 of the GAMP® 4 Guide.³ This simple model also is being used in areas of risk assessment other than computer systems, and this is perfectly acceptable given the non-proscriptive nature of the ICH Q9 Consensus Guideline.

For the sake of this article, the following terms also will be used and these are taken from the GAMP® 4 Guide:

- risk impact
- risk likelihood
- risk classification
- probability of detection
- risk priority

To aid the reader, defined terms are italicized throughout the text in the remainder of this article.

The Process of Risk Assessment

It is important to understand that *Risk Assessment* is a

systematic process where individual *Hazards* are identified, analyzed, and evaluated. Although sometimes used synonymously, *Hazards* and *Risks* are different.

A *Hazard* is a potential source of *Harm*, which is identified during *Risk Identification* (where *Harm* is used in the sense of damage to patient health). During the *Risk Identification* step, multiple *Hazards* may be considered in a single context such as trying to identify *Hazards* associated with a particular stage in a manufacturing process or the *Hazards* associated with a specific clinical trial.

Experience from a number of IT projects confirms that it is practical to group together similar *Hazards* during the *Risk Identification* process and the term ‘risk scenario’ has been defined. This collection of *Hazards* can then be assigned to an individual or team who will then be responsible for completing the *Risk Assessment* and *Risk Control* processes for the specific risk scenario.

Risk is the combination of the severity of the resultant *Harm* combined with the probability of the *Harm* occurring.

Severity of *Harm* is equivalent to the GAMP® models *Risk Impact* and the probability of the *Harm* is equivalent to the GAMP® models *Risk Likelihood*. Because *Risk* is the combination of the severity of the resultant *Harm* combined with the probability of the *Harm* occurring, *Risk* is synonymous with the GAMP® models *Risk Classification*, which is derived from the *Risk Impact* and *Risk Likelihood*.

There is often confusion over the terms *Risk Assessment*, *Risk Analysis*, and *Risk Evaluation*. As defined in the terms above, *Risk Assessment* is an overall process. *Risk Analysis* involves a relative estimation of *Risk*, and *Risk Evaluation* uses a more quantitative or qualitative determination of the risk.

Since *Risk* itself is a combination of two factors (severity of the resultant *Harm* combined with the probability of the *Harm* occurring), the estimation of *Risk* infers that both factors are considered during the estimation process. Practical problems may arise when estimating *Risk*, because only the severity of the *Harm* is considered and the probability of the *Harm* occurring is ignored.

This is often a practical problem encountered by quality, regulatory, or clinical members of staff who are often concerned with worse case scenarios (i.e., what might or could happen) and not what is likely to happen.

The GAMP® model also has a concept of *Probability of Detection* which is not included in many *Risk Assessment* processes. However, it is a useful idea because it recognizes that there may be a significant delay between the *Hazard* occurring and the resultant *Harm* to the patient.

Although the *Hazard* of mistakenly adding no active ingredient during the formulation of a drug product may have occurred, this can be detected (by QA analysis of the final product) prior to the *Harm* (due to the lack of availability of an effective product for a particular patient) occurring.

This is often excluded from many formal *Risk Assessment* processes in other industries which deal with more significant *Harm* severity. This is because of the almost immediate cause and effect relationship between the *Hazard* and the

Harm occurring, e.g., failure of fly-by-wire software as an aircraft is on final approach for landing or a failure of containment of a toxic chemical during manufacturing.

On a relative scale of *Harm* severity, most processes within the life sciences industry are low when compared to industries such as the nuclear industry, chemicals, and aeronautical. This should be kept in mind by both manufacturers within the life sciences industry and their regulators. Although the potential of *Harm* to patients can not be ignored, perhaps the most critical areas in terms of immediate *Harm* to human life are some of the manufacturing processes used to make APIs or other chemical intermediates (process hazard).

It is easy to get confused by the different terminology, and reading the paragraphs above and referring to Figure 2 will help show the relationship between these terms.

Risk Control

The second part of Risk Management is the effective reduction of risk. Assessing risks is of no value and may well waste time and money if the output of the *Risk Assessment* process is not used to effectively mitigate risks.

Risk Reduction is the process of taking action to reduce the probability of the occurrence of *Harm* and/or the severity of the *Harm*.

Risk Control is the process of taking action to implement risk management decisions, not just those associated with reducing the probability of the occurrence and/or the severity. This may include steps to review risks on a regular basis or to ensure that they are effectively communicated, that personnel are trained to recognize that risks have occurred, and implement immediate corrective actions. Therefore, *Risk Reduction* can be thought of as a subset of broader *Risk Controls*.

In the GAMP® model, there is also a concept of *Probability of Detection*. In the strictest sense (as defined in ICH Q9), *Risk Reduction* does not address this issue, but it is possible to identify and implement *Risk Controls* that will increase the probability of detecting that a *Hazard* has occurred, prior to it causing a resultant *Harm* to the patient.

Risk Communication and Review

Risk Communication is an important step during which the outputs from the risk management process are made known to a wider community. This in itself can help in the recognition and effective control of risks.

Risk Review steps should be conducted on a planned basis and take into account new information, knowledge, and experience and may consider whether or not new *Hazards* have been introduced as a result of implementing previous risk controls, as per ISO 14971.

Combining all of these elements provides the overall risk management model in ICH Q9, which is reproduced in Figure 3.

How Real is the Risk?

Before starting a risk management process, it is important

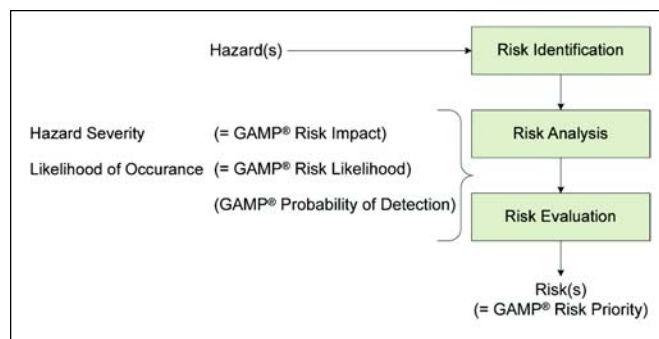


Figure 2. Risk assessment process, as per ICH Q9 (with equivalent GAMP terms).

that industry professionals understand the real risks they are dealing with. Subject Matter Experts (SMEs) often focus on their areas of expertise and forget that the real risk of regulatory concern is due to the nature of the product, the quality of the product, and the potential of *Harm* to the patient.

Therefore, it is important to understand the modality of the drug or the class of a medical device, how it interacts with the patient, and the extent of the resultant *Harm* to the patient.

To be able to effectively use risk management as a business tool, we must become familiar with assessing the real (if potential) *Harm* to our patients and acting accordingly.

Similar to the nuclear, chemical, and oil and gas industries we must become comfortable with the fact that there is a limit to what companies can and will spend to avoid *Harm* to our patients. While medical device professionals are used to classifying *Harm* to patients, this is much less common in the pharmaceutical sector and there are useful lessons to be learned from the medical devices sector.

Process Hazard versus Patient Harm?

Complicated R&D, manufacturing, and distribution processes make it easy to consider the short term (immediate) process hazards, but often make it difficult to consider the consequential harm to patients

As an example, a process engineer would be quite rightly concerned about the risks of a plant explosion and the immediate potential *Harm* to fellow employees and other members of the community (the process hazard). However, should the worst happen and the plant explode, the probability of detecting that the *Hazard* has occurred is high and there is little likelihood of any *Harm* to any patients.

Likewise, although a fire or a flood in a computer data center is a very real concern to the IT group, the chances of this having any real impact on product quality or the patient are low.

Nevertheless, it is important that the risk management of both of these scenarios is considered. *Hazards* that could lead to these situations are numerous and it is important that all of these *Hazards* are considered and addressed in relative terms, within the context of the local risk scenario.

In terms of *Risk* to product quality or the likelihood of causing *Harm* to a patient, all of these *Hazards* are a rela-

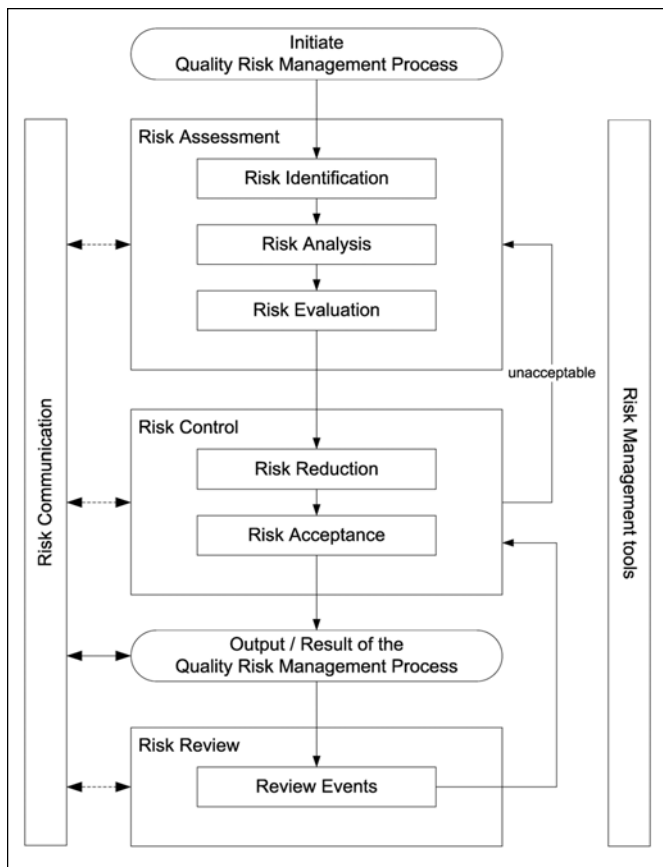


Figure 3. Overview of ICH Q9 quality risk management process.

tively low risk. Therefore, it is important when assessing any risk scenarios, each of the *Hazards* within the risk scenario is considered both relative to one another, and also in the context of overall *Risk* to product quality and potential *Harm* to patients.

On a recent Enterprise Resource Planning (ERP) system project, members of the IT infrastructure group struggled to understand that a failure of the computerized systems was a risk scenario (collection of *Hazards*) that should be considered in terms of patient *Harm*. In their experience, a failure of their IT Infrastructure impacts solely on the software applications with no consideration of the consequential impact on patients. In a situation like this, it is apparent that this will cause confusion between the difference between a *Hazard* and a *Risk* and what should be done about such *Risks*.

The key point is that one person's *Risk* might be another person's *Hazard*, depending on whether the incident being considered is a risk to a local process or a risk to product quality and patient safety.

In industries where the *Hazard* severity is higher, it is often easier to link the *Hazard* with the resultant *Harm*. This is because the *Hazard* occurring and the resultant *Harm* are much closer in time. When an airplane crash occurs, things happen quickly. When a chemical plant has a release of a toxic chemical, the consequences soon become clear.

In life sciences, this is more difficult because of the longer time scales and the complex interaction between hazards and the risk to product quality and patient safety. Where a

complex chain of consequences across the organization leads to the risk to product quality or patient safety, it is difficult for individuals to consider the real risk. For example, it may be years or decades before the risks associated with a poorly designed clinical trial are identified.

Experience has shown that the effective *Risk Assessment* processes need input from a mix of SMEs. When determining the *Hazard* severity (or *Risk Impact*), it is often the case that members of the quality or regulatory affairs group are more familiar with the quality criteria of a specific product and how the product interacts with the patient. Such individuals are usually much better suited to the determination of *Hazard* severity or *Risk Impact*.

However, when determining the *Risk Probability* or *Probability of Detection*, it is usually SMEs who are closest to the *Hazard* who better understand the likelihood of the *Hazard* occurring and how easily it may be detected.

Therefore, the overall process of *Risk Assessment* is most effective when a combination of SMEs are included or consulted. This may be achieved by a desk review or by a collective *Risk Assessment* process such as a workshop to identify *Hazards* and to determine the resultant *Risk Priority*.

Because of the qualitative or quantitative determination of risk by *Risk Evaluation*, this can be conducted as a stepwise process with quality, regulatory, or clinical experts first determining the *Harm* severity (or *Risk Impact*) and technical SMEs then determining the *Risk Probability* or *Probability of Detection*.

Because *Risk Analysis* only determines *Risk* on a relative basis and does not make use of documented qualitative or quantitative output, but should nevertheless consider both the *Hazard* severity and likelihood of occurrence (*Risk Impact* and *Risk Likelihood*), it is more difficult to conduct a *Risk Analysis* as a desk exercise.

Experience from large IT projects confirms that relative *Risk Analysis* can best be conducted as a workshop with all SMEs playing a part. On one project (the *Risk Analysis* of an existing data center where an existing ERP system was being rolled-out to a new site), the workshop identified a wide range of practical *Hazards* that had previously been overlooked.

Local versus Corporate Risk

Subject matter experts, by definition, have many years of experience and for some, it is second nature to mitigate risks as part of the design process. As an example, a process engineer will automatically think about safety in terms of prevention, detection, and containment.

For immediate risks in terms of safety (process hazard), health, and environment, there may be other regulations that require risk, safety, or environmental impact assessments to be conducted and documented. However, this may not include any regulatory risk assessment, which includes consideration of *Risks* to product quality and potential harm to the patient.

Similarly, an IT professional may automatically think about redundant processors or redundant disk arrays without necessarily considering or documenting that these design

aspects are intended to mitigate *Risk*. It is also likely that when these issues are considered, they are considered in terms of IT service levels rather than potential *Risk* to product quality or *Harm* to patients.

Many *Risk Controls* will be considered as part of the design, but it may be the case that the documentation of the *Hazards* is overlooked, because the design process includes *Risk Controls* as standard.

Projects conducted within the last three years have shown that it is possible for *Risk Assessments* to assess each *Hazard* in terms of the relative *Risk* within the local risk scenario (such as process hazard or loss of IT service) and also against a corporate scale of a *Risk*, which considers product quality and potential *Harm* to patients.

This will then inform:

- the local department how much of their own time, effort, and resources should be spent on their own *Risk Controls*
- the relative importance of the local department on overall regulatory risk, the resultant relative impact on product quality and patient safety, and whether more (or less) corporate time, effort, and resources should be spent addressing such regulatory risks

Looking to the future, organizations looking to take a practical, holistic approach to risk management will need to first determine their overall approach to risk management with regard to product quality and patient safety and ensure that different, local methods of risk management within the organization are mapped relative to a standard corporate approach.

This will allow all risks in the organization to be assessed on a relative basis and for scalable and appropriate risk controls to be identified. This will ensure that resources are

appropriately assigned and that *Risk Controls* and *Risk Reduction* activities are focused on value added activities which effectively mitigate risks.

Is It Worth It?

Due in part to increased regulatory focus, there is currently a great deal of interest in risk management. There is also a genuine belief that *Risk Assessment* can effectively assign resources and reduce costs by reducing the extent of non-value added activities, i.e., reducing or eliminating those activities which do not effectively help to mitigate risk, which can be identified as part of the *Risk Review* process.

In some cases, the use of risk management techniques from other industries has over complicated things and added to costs. When complex and detailed *Risk Assessments* take more time and money than can be saved by a reduction in non-value add activities, or where such activities do not help in effectively controlling risks, it is worth asking the question ‘is it worth it?’

As one example, prior to the publication of the GAMP® Good Practice Guide: *IT Infrastructure Control and Compliance*, one organization was using a nine stage risk assessment of IT Infrastructure. However, because IT Infrastructure usually uses mature standard technology with only an indirect impact on product quality this should now be considered to be unnecessary.

Preliminary Hazard Analysis

A Preliminary Hazard Analysis (see ICH Q9, Annex I.7) is all that is needed to determine an appropriate approach to IT Infrastructure *Risk Assessment*. In most cases, this confirms that a simple *Risk Analysis* process is all that is needed and that a complex *Risk Evaluation* of each component of IT Infrastructure is unwarranted.

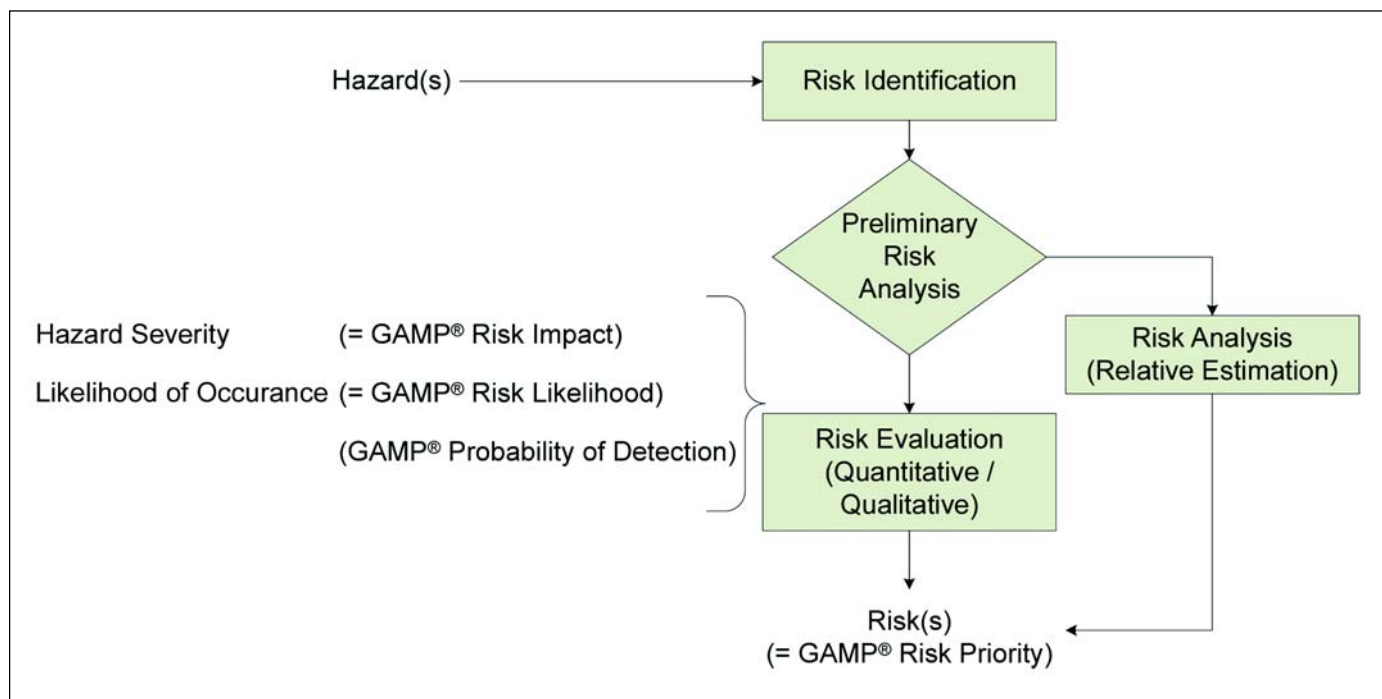


Figure 4. Scaled risk assessment process with preliminary risk analysis.

It must be emphasized that the use of *Risk Evaluation* is more appropriate for large, complex processes or systems, or those where a Preliminary Hazard Analysis indicates a greater *Harm* severity.

In terms of a manufacturing process, there will be many stages, only certain of which have a direct impact upon product quality and resultant patient safety. A Preliminary Hazard Analysis will indicate that simple *Risk Analysis* might be used to determine the relative risk to product quality of each stage in the manufacturing process, and a more detailed *Risk Evaluation* is required only for the quality critical stages (or hazard control points), in order to identify the quality critical parameters and identify potential and specific *Hazards*.

Experience from a number of ERP system or Laboratory Information Management System (LIMS) projects also confirms that for large, complex applications, out of the hundreds or thousands of requirements, a relatively small proportion have High *Risk Impact* or High *Risk Priority* and it is useful to focus validation efforts on these functions.

Preliminary Hazard Analysis helps to identify those areas where a more formalized *Risk Evaluation* process may be required, but for most areas that do not impact product quality, a relative *Risk Analysis* is all that is required. Therefore, the Preliminary Hazard Analysis supports risk

based validation, helps to control costs, and makes risk management practical.

Enterprise Wide Risk Assessment

While a relativistic *Risk Analysis* process often works well in a local risk assessment, the lack of qualitative or quantitative criteria means that these can often be subjective.

Requirements gathering for enterprise wide IT projects show that different professionals within the organization think about risks in different ways. As an example, while members of the business may assess the risks inherent within the distribution chain consistently in relative terms, it is unlikely that they also will be able to determine the relative risks of such hazards against those in research and development or in manufacturing.

While there is an obvious attraction in considering *Hazards* on a simplistic, relative basis across the organization, the added value of a qualitative or quantitative *Risk Evaluation* is it that allows important *Hazards* to be considered in detail.

Figure 5 shows a schematic approach where different *Hazards* are considered in the context of a specific product, a local system, or process based risk assessment and an overall corporate risk assessment process.

It shows an example of risk assessments being conducted on two medical devices, a manual training process, a quality system, and an automated process control system used in manufacturing. This may be applicable to a large life sciences company manufacturing both pharmaceuticals and medical devices.

For each of these areas, a Preliminary Hazard Analysis would be conducted to determine the relative *Hazard* for the product, system, or process. This considers the worst case impact to product quality and consequential (or in the case of the medical devices direct) *Harm* to the patient.

For medical devices, an ISO 14971 derived *Risk Assessment* process would be used to consider the specific *Hazard* severity and likelihood of occurrence for each *Hazard* (note that many *Hazards* will have a lower severity than the worst case determined in the *Preliminary Hazard Analysis*). However, for the Class I medical device (with a Low overall Hazard Severity), a relative *Risk Analysis* approach is taken and for the class III medical device a more rigorous *Risk Evaluation* is conducted. This gives a 'Device Risk' for each *Hazard* considered.

In the case of the manual training system, a simple, organization specific *Risk Analysis* is conducted. This considers the *Hazard* severity, likelihood of occurrence, and also 'borrows' the GAMP® concept of *Probability of Detection* to produce a System Risk for each specific *Hazard* considered.

For the quality system, an ICH Q9 *Risk Assessment* is conducted. Because the quality system was determined to have a worst case High Hazard severity during the Preliminary Hazard Analysis, a quantitative/qualitative *Risk Evaluation* is conducted. This considers the specific *Hazard* severity and likelihood of occurrence for each *Hazard* and again arrives at a System Risk for each *Hazard* considered.

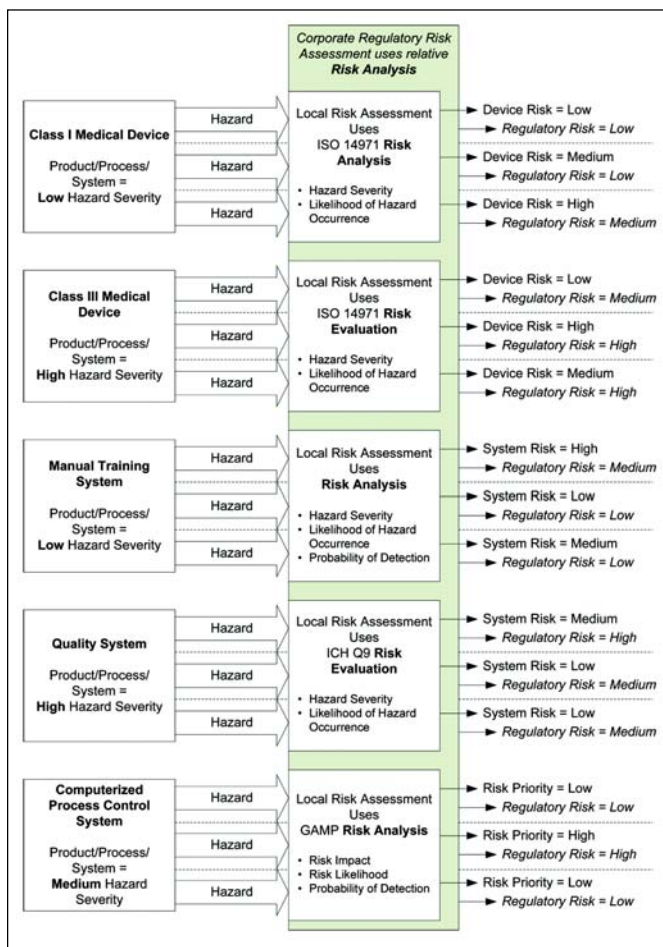


Figure 5. Schematic of risk assessment process combining local product/process/system risk with regulatory risk.

Finally, for a computerized process control system, the GAMP® risk assessment process is used to consider *Risk Impact*, *Risk Likelihood*, and *Probability of Detection* for each Hazard. Because the Preliminary Hazard Analysis determined that the worst case *Hazard* severity was Medium, a relative *Risk Analysis* is used to produce a *Risk Priority* for each *Hazard* considered.

Using different methods for different products, processes, and systems is possible, and allows local teams to distinguish their own risks at a more granular level and allows the appropriate allocation of local resources. It also is possible to consider all of the *Hazards* on a consistent and relative basis across the organization.

Using a combination of the worst case Hazard Severity derived from the Preliminary Hazard Analysis and the local risk (Device Risk, System Risk or *Risk Priority*), it is possible to consider each Hazard on a relative scale of regulatory risk at the Enterprise level. This is shown in Table B.

Deriving the regulatory risk this way does magnify the effect of the *Hazard* severity (the worst case *Hazard* severity for the product, system, or process is combined with the *Hazard* specific severity), but this does provide a consistent basis for considering relative risk to product quality and patient safety across the organization.

However, by comparing different products, processes, or systems, any qualitative or quantitative consistency is lost and this enterprise wide process must be considered a relative *Risk Analysis*. Nevertheless, it may be useful when considering where to allocate resources at a corporate level in order to most effectively mitigate risk.

Without such a consistent scale of regulatory risk, inconsistencies arise. On one project (updating and validating analytical instruments in a laboratory), it was discovered that twice as much time and money had previously been spent validating instruments in product development when compared to product manufacturing. This was obviously inefficient and unjustifiable on the basis of relative risk and was highlighted using a system such as the one described above.

Conclusion

There are a number of risk management methods that can be used and each of these has advantages and disadvantages. While there are effective risk management models available from other industries, care should be taken when considering adopting these for use in life sciences, because of the danger of overcomplicating risk management.

Organizations need to have a clear and consistent view of the risk management terminology that will be used and how different risk management processes are aligned across the business.

As seen from some of the examples above, this can be difficult to achieve across different areas of the business. However, in order to reduce risk to product quality and patient safety and in order to most effectively use resources (including money), it is well worth life sciences companies investing in their understanding and development of consistent risk management processes.

Worst Case Product/System/Process Hazard Severity (from Preliminary Hazard Analysis)	High	Medium	High	High
	Medium	Low	Medium	High
	Low	Low	Low	Medium
		Low	Medium	High
Product Risk, Process Risk, or Risk Priority				

Table B. Regulatory Risk Priority (derived from Product, System or Process Hazard Severity, and specific Hazard Risk).

Organizations should consider providing guidance on when it is useful for local departments to conduct a simpler *Risk Analysis* or when a more complex, but consistent *Risk Evaluation* should be conducted. In developing such guidance, organizations should consider the time and cost of conducting *Risk Assessments* by different methods against the time and cost that will be saved as a result of focusing on high risk priority areas and the effective mitigation of such risks.

Just as chemical engineers automatically think about process hazards and their mitigation as part of the design of a new bulk pharmaceutical plant, risk assessment and risk management can be integrated into almost any activity, as long as the process and each of the elements is well understood and aligned with the appropriate project activity.

This use of a Preliminary Hazard Analysis in this context can be very beneficial. Based on experience on IT projects, risk management can be built into standard project activities without requiring significant additional effort to assess or mitigate risks. Comparing applications of similar size and scope, the introduction of practical risk-based validation into large, complex IT projects has seen the cost of validation fall from around 25 to 30% of project budgets in the late 1990s to around 10 to 15% in recent years.

When properly documented, a simpler *Risk Analysis* will often be appropriate. Experience from IT projects is that *Risk Analysis* typically takes 30 to 50% less time and resources than qualitative or quantitative *Risk Evaluation*; but that a simpler and lower cost *Risk Analysis* can provide the same benefits in terms of risk mitigation in many functional areas. The use of more complex *Risk Evaluation* approaches should be reserved for risk scenarios that have a specific and direct impact upon product quality and patient safety.

Resources can effectively be focused as a result of *Risk Assessment*, based on a local, context specific determination of risk and an enterprise wide understanding of overall risk. However, this does require the development of a consistent risk model across the whole organization.

In conclusion, experience from IT projects has shown that practical risk management is achievable, can save costs, and effectively mitigate risk. *Risk Analysis* can be applied in other areas of the business that only have an indirect impact on product quality and patient *Harm*, but detailed *Risk Evaluation* is still required for quality critical activities, as per ICH Q9.

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About the Author



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As Chairman of the GAMP® Testing Special Interest Group, he has helped establish the value of risk-based testing in the field of computer systems validation; he has helped a number of life sciences organizations to develop their risk management models, and provides training on pragmatic risk management. Stokes can be contacted by e-mail at: david.stokes@businessdecision.com

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This article presents a logical way to begin implementing PAT projects within an organization with an objective focus on return on investment based on process expertise, facts, and data.

Process Review for PAT – Selecting Cost Efficient PAT Projects

by Alex Brindle and Per Vase

Introduction

Process Analytical Technology (PAT)¹ has been talked about for several years as the sorely needed shot in the arm that both development and manufacturing need to increase innovation, improve quality, and reduce costs in the pharmaceutical industry. The anticipation of PAT, within just a few years of coining the terminology, is already huge.

After all, the whole point of PAT is to ultimately provide benefit to the patient. If a manufacturer, through PAT, can save money in production this will ultimately affect the company's profitability and the amount it can spend on finding new drugs. An improvement in quality means an improved product delivered to the patient. Less regulatory burden means the authorities can concentrate their efforts on manufacturers who are posing risk to patient safety. PAT is there to assist manufacturers make better products more efficiently, though

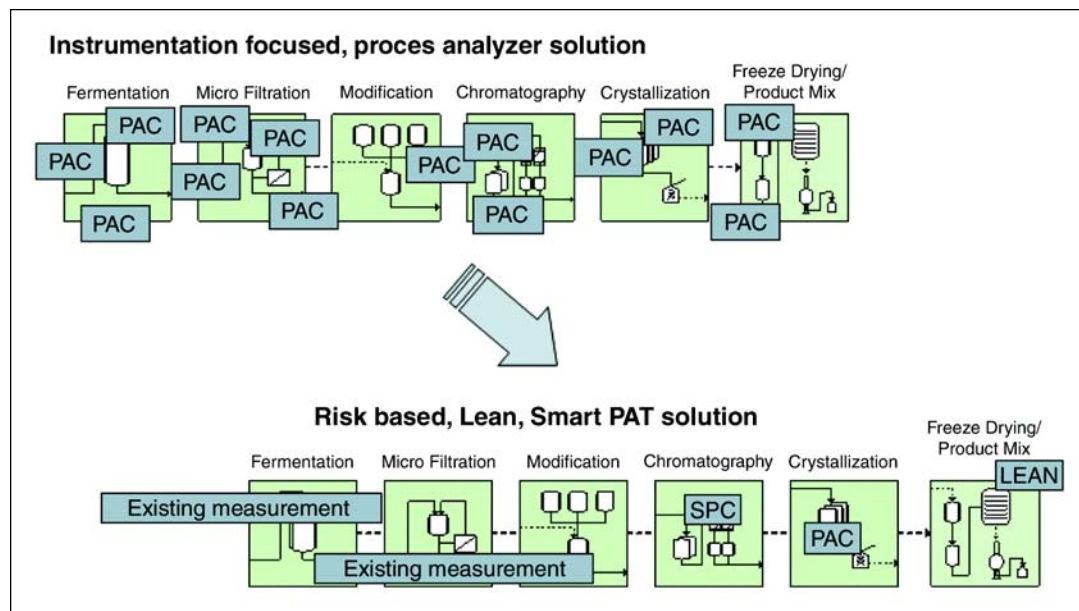
the real winner will be the general public.

However, the widespread implementation of PAT has been slow despite the potentially huge financial advantages and regulatory flexibility.

There are a number of reasons for this; the different skills needed to complete PAT projects, caution about trying something new ('we make a profit now so why change it'), and crucially for this article - the inability to objectively select PAT projects and quantify their benefits compared to their costs.

When trying to persuade people to spend money on PAT projects, they will want to know whether the money they are spending is a good investment and if it is being spent in the right area. Management doesn't want to blow the budget on an employee's hunch or favorite PAT technology, which could turn out to be a turkey; but they will release budget if they can clearly see the advantages compared to the costs and that these have been defined using objectivity

Figure 1. Before and after. Before - one person's suggestion (an expert in PAC - hence the heavy use of PAC solutions) on how to improve a line using PAT. After, the use of the Process Review using a balanced team has removed this bias and only suggested projects which provide real value.



and supported by facts and data. The easiest way to get money for any PAT project is to show that it actually funds itself in benefits and that it is the best use of funds compared to all the other competing projects in an organization.

A good way to do this is a Process Review for the following reasons:

- PAT projects will be selected and prioritized in terms of biggest benefit and not on people's preferences for particular technologies or process steps.
- A team will collectively understand processes much better than any one process expert; therefore, problem areas can be identified (if they can be solved this obviously gives the biggest benefits for the lowest costs).
- A team-based approach will be more *objective* than the *subjective* opinion of an individual.
- PAT projects should be selected on team intelligence *and* facts and data.
- The Process Review will cost a tiny fraction of the PAT projects implemented. Spend a small amount of money up front to get it right.
- The Process Review will avoid wasted effort on non-value added activities.
- There will be a sense of involvement of all functions and representatives of areas.

The Process Review can be applied to any type of process, it does not matter whether it's an upstream process for a niche biotech company or a secondary process for a top five pharmaceutical company - the same guidelines apply - it will just be the people who should be drafted into the team who will change.

It is only natural for scientists and engineers (and these are usually the people suggesting the PAT projects) to want to pursue technically challenging projects which *are of interest to them*. This can lead to technology heavy and overcomplicated solutions when simple

will do. It also can lead to the favoring of certain process steps even though the bigger benefits are elsewhere.

The top diagram in Figure 1 shows what happens when an entirely technology driven, Process Analytical Chemistry (PAC) solution is used on a process. In this example, the first suggested PAT project was to attach process analyzers to every step of the process simply because the technology existed and could measure something rather than the benefit it provided. In essence, many of the solutions solved a problem that did not exist, or were far too expensive and complex for the problem solved. The end result was an overly expensive PAT project compared to the benefits it provided - management was not interested in spending all that money for the limited benefit.

Using the Process Review led to a smarter, cheaper, and more beneficial solution presented in Figure 1. A team based approach has led to a balanced view and removed the obsession with buying process analyzers for everything. PAT technology is suggested for areas where they provide real benefit compared to their cost. The analysis of existing data in the process review revealed that existing measurements could be used to improve understanding and control. In fact, on one of the process steps, it was realized that a lean project would provide much more benefit compared to the costs rather than a PAT solution so this also was implemented.

The end result was that management easily approved the projects suggested after the Process Review, because they provided all the benefit for a fraction of the cost of the initial project suggestion.

An objective selection of beneficial (financially and otherwise) projects can be selected in the following three steps.

1. Process Overview – understand the whole process to know what you are dealing with and how to focus on the biggest problem.
2. Data Analysis – back up your objective opinions with data analysis.

3. Prioritize – select your projects taking into account their expected benefits (financial or other wise) and expected complexity (which will essentially be related to effort, risk, and cost).

Step 1 - Process Overview *Select the Right Team*

Typically, there are several experts within an organization which will know a great deal about an individual process step. There will probably be some people who know the overall manufacturing process well and how the individual steps link up; but they are unlikely to know these steps in great detail. There will be people who know the quality delays and issues. There will be people who operate the process every day and know things that even the top process scientists don't know. A PAT expert will know which PAT tools can be used to solve the process issues. By pulling all these people together there is a team that understands the overall process in depth and the issues surrounding it. This is a completely different approach to contracting with an expert who supposedly knows a lot about processing. Instead, a facilitator is used to harness the companies own intelligence.

There are some guidelines to follow when performing a process review though it is not a one-size fits all approach. The following guidelines can be adapted to fit the situation being reviewed.

Guidelines for the Right Team

This should be a combination of operators, manufacturing engineers and scientists, development engineers and scientists, PAT specialists, and people with an overview of the entire process. It cannot be overemphasized enough that this is not an exercise for an exclusive set of managers; people who actually work the process should be involved.

This 'right team' may include people who have not seen the actual process before, but who have other experiences. It is important that these individuals get an opportunity to 'walk the process' so they get an understanding of what

they are dealing with in terms of how the process is run on a daily basis.

Run a Process Mapping Workshop with the Right Team

One of the crucial goals of this step is to get the complete process, and how it really runs down on paper. There may be some people within an organization who understand the complete process well (and they will be very useful here), but they are the exception and not the rule. By using team intelligence, it will be possible to map the entire manufacturing process from start to finish. This mapping should not be a chemical engineer's drawing where only certain people can understand the diagram. This map is to be accessible to everyone and should use simple blocks to describe the process flows, actions, and checks that occur. An example is given in Figure 2.

With the map drawn on a piece of paper (preferably a large piece of paper so people can gather around it), problem areas within the process can be discussed. The facilitator will come in useful here at initiating these discussions and also halting them so that all issues can be discussed suitably. There are many techniques for discussing and recording issues with processes; the author likes to work to the keep-it-simple principle and tends to just use post-it notes.

It should then be possible to discuss some PAT applications which will help solve these problems. For example, if there is a problem with variability in connection to one of the process steps then a Statistical Process Control (SPC) project would be suitable. If a processing step has variable output, because it is difficult to control with what is in place then the implementation of additional hardware, such as a process analyzer, would be a suitable project.

The process mapping workshop should typically take one to two days depending on the complexity of the process.

Run a Product Quality Workshop with the Right Team
The purpose of the product quality



Figure 2. Mapping the process is a team effort. It is important to understand the overall process before the relative value of different PAT projects can be assessed.

workshop is to identify important final product quality characteristics and possible factors influencing these final product characteristics.

The first stage is to identify the final product characteristics and what their importance level is.

The second stage should seek to identify why these listed characteristics are so important. It will be learned that these characteristics are listed as important because of regulatory guidelines, internal specifications relating to product quality, or other consider-

ations. The why question should continue to be asked. Why are the listed specifications important? It is often the case that internal specifications are in place for historical reasons and do not improve product quality or reduce risks.

By working back into the process from these final product characteristics, it should be possible to identify which controllable factors influence the final product characteristics. It should be noted how these characteristics are controlled today and ultimately how

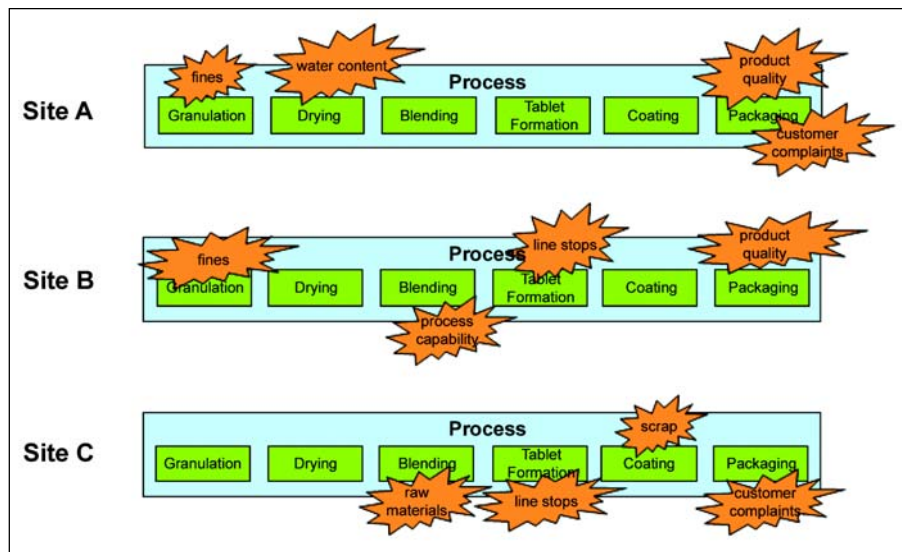


Figure 3. An example of the results of collecting opinions for overall issues at three different sites - note that this is exactly the same process for the three different sites - the sites have some issues in common and others that are individual to that site.

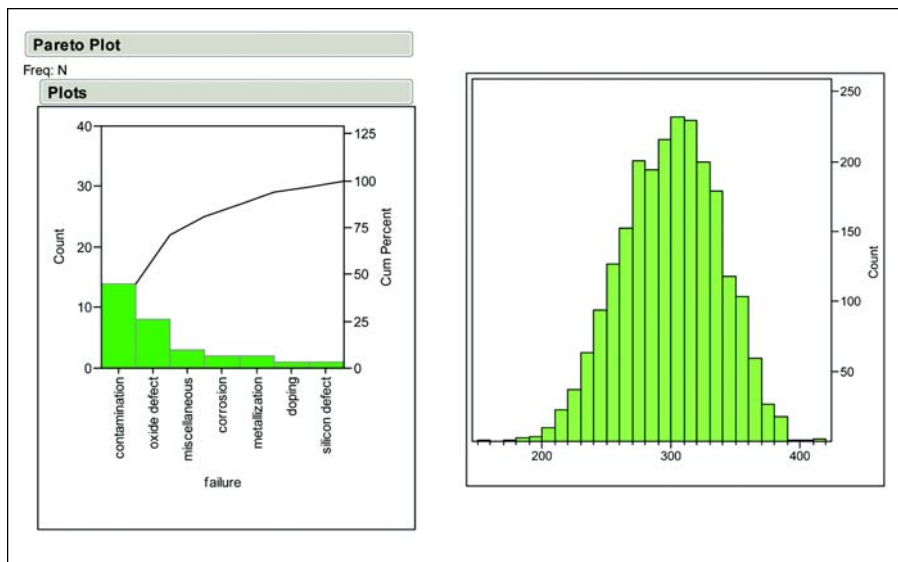


Figure 4. Examples of a Pareto plot and histogram.

they could be controlled in the future.

Again, the facilitation process is useful to encourage debate and reach objective conclusions. To help the process, root cause analysis tools such as Ishikawa diagrams or the five why's technique² can be used to help the team come to grips with the real issues rather than just scratch the surface.

The result of combining these two workshops will be an objective list of current problems associated with the process and some ideas about how these can be overcome in the future. This list will be used to help lead the data analysis used in Step 2 of the Process Review.

An example of this is shown in Figure 3. The same process was present at three different manufacturing sites. A number of major issues were identified at each site that PAT projects could be used to overcome. Amazingly (but typical in the author's experience), the issues for the different sites aren't always the same. This demonstrates the importance of the data analysis stage in Step 2 to actually review these objective opinions and prove the true underlying issues.

Step 2 - Process Data Analysis

Step 1 will have used team intelligence to objectivity list and define some of the issues apparent with the manufacturing process quickly and efficiently.

However, all of this is still an opinion (even though it is the most objective opinion) and must be transformed into the real situation. To do this, data must be collected, transformed, analyzed, and converted into facts.

This data focused stage will of course benefit from the outcome of Step 1. Step 1 can be seen as a way of screening ideas in order to focus the data analysis stage on some key issues – without this, there would be far too much data to analyze. The combination of people, ideas, instincts, and opinions, and their subsequent data analysis is both quick and fact based.

This data focused stage will critically require an industrial data analyst experienced in historical analysis, because most organizations have a lot of data, but are not using it for several different reasons:

- data records are incorrect
- data is incomplete
- data is unstructured
- data is difficult to access
- lack of data analysis tools
- lack of data analysis capabilities

Incorrect data records and lack of use of data goes together. All data acquisition systems, whether manual or automatic, suffer from the possibility to record incorrect data. This may be measurement uncertainty, typing errors, instrumentation errors, and so

on. Unless data is continuously used to increase the chances of discovering and correcting errors, the usefulness of the recorded data will automatically degrade rapidly with time.

Therefore, the data of interest must be reviewed for correctness and a decision made to correct or exclude incorrect data from the Process Review. If there are limited amounts of data, this can be done simply by reviewing the data, individual record by individual record. If there is an extensive amount of data, this is likely to be very time consuming. In this situation, the use of different kinds of statistical outlier tests,³ to find extreme values not belonging to the general population, should be possible if the data is structured.

Data is often useless because of too high a measurement uncertainty. It is often a good idea to perform a fast measurement system analysis,⁴ at this stage, to see if variability in the data is not caused by the measurement system itself. If this is the case, the measurement system analysis will give a good guidance on where to improve the measurement system after which recollection of data will be required if it is to be used.

Incomplete data is another typical problem when collecting data. Sometimes the missing data can be obtained from other parts of the organization or from other files. If this is not the case, recollection of process data might be necessary.

Unstructured data is difficult to convert to information. The analysis to be performed later is very much based on finding relations between different sets of characteristics. For this to be possible, the data not only needs a given quality characteristic, but also metadata (data on data) like machine identity, operator identity, time, raw material batch, environmental conditions, recipe, etc. Ideally, the data should be organized in a database structure. If the data is available electronically, it can be converted into a database structure for subsequent analysis. If necessary, data can be converted from paper records, but this is obviously time-consuming compared to elec-

tronic records.

When data is made electronically available, it can be converted to information. This can be done using descriptive statistics, where data is plotted in different types of charts (e.g., Pareto charts or Histograms⁵) without performing statistical calculations. Just by plotting data, many relations between problems and solutions will become obvious. Examples of these types of simple data analysis are presented in Figure 4. The Pareto plot simply shows the major contributors to the cause of failure for a specific part of a process. The Histogram can give fast overview of data and shows if a problem is caused by level, variance, or outliers. The advantage of these techniques is that they are very visual and require no calculations. They can easily be understood by everyone. The plotting of data can be done in all standard spread sheet software, but this is easier using dedicated statistical software tools if future statistical analysis is required.

The simple information available at this stage may be sufficient to proceed to Step 3 of the Process Review if the process is relatively straightforward and the data firmly backs up the objective opinions from Step 1.

However, if the process is complex and the picture less clear, further analysis may be necessary to help understand what the major issues really are and which projects should be considered.

A more detailed statistical analysis to find the rest of the information hidden in the data will help in this situation. A larger industrial statistical tool box (Regression, Analysis of Variance, Statistical Process Control⁵, etc.) should now be used. These tools can extract causes of systematic variation from random variation. Systematic variation can be removed by simple process adjustments, while random variation can only be reduced by re-optimization of the process. Although the calculations behind a statistical control chart require some statistical expertise, the outcome of it as shown in Figure 5 is easy to act on by everyone. If data is within the red control limits, the pro-

cess is in control and no adjustments should be made. If data is outside the control limits, the process has changed so adjustment and/or maintenance of the process should be considered.

Several years ago, the use of these statistical techniques had been limited to statistical experts, but today easy to use software tools are available. The success of using these tools no longer depends on a person's statistical capabilities, but more on practical experience in using the tools to solve problems. It takes years of practical experience to become a good practical statistician so make sure the right person is on the team. If the data is of multivariate character, multivariate tools like Prin-

icipal Component Analysis and Partial Least Squares⁶ have to be used.

After having performed the statistical analysis, it will be known whether the level of random variation is sufficiently low, and therefore, if the process is capable. If not, the correlation studies will indicate which sources of variation will need to be focused on. It also will become apparent as to whether the process is predictable (or in statistical control). A process needs to be both capable and predictable.

The final results of the data analysis stage will be the following:

- confirmation or rejection of the processing issues identified and dis-

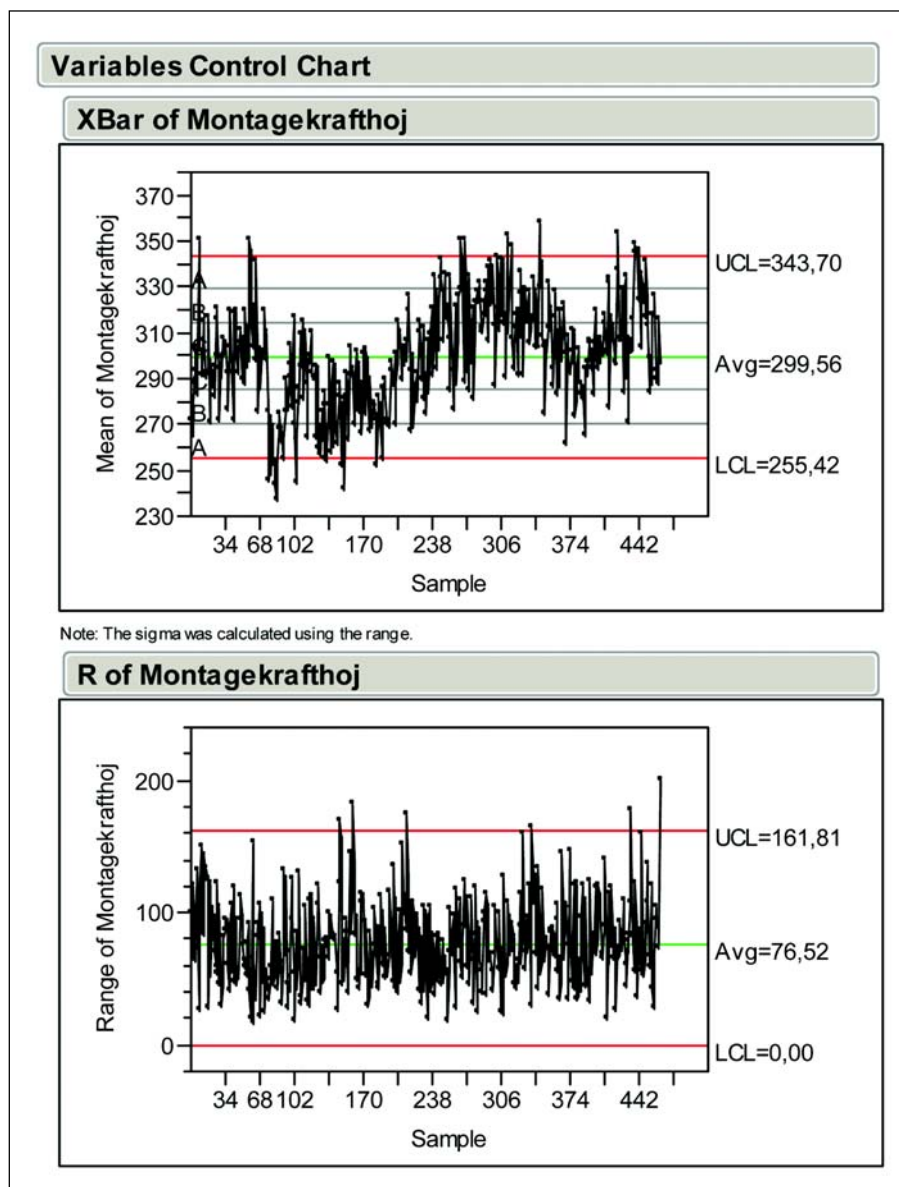


Figure 5. Statistical control charts.

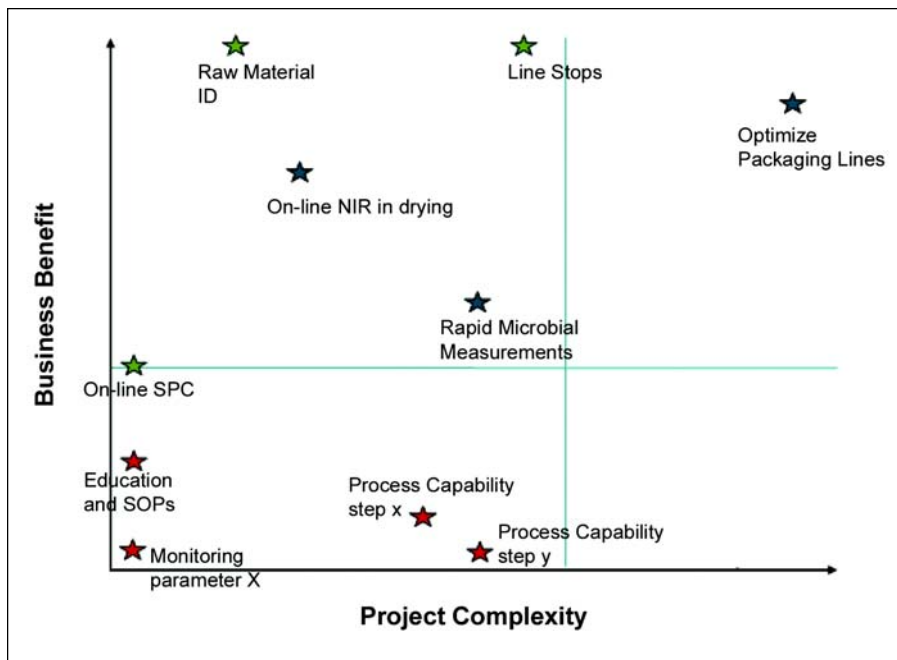


Figure 6. A real-life example of project prioritization.

issues that people didn't realize existed.

There will be a list of maybe 10 to 20 problems that could be solved using ideas from PAT. The question now is how to select which ones go ahead first. First, one should consider the benefit of solving that particular problem; yes money always features in any benefit analysis of this kind, but it is important to decide what features of success could be viewed as benefits. One might consider:

- money saved each year
- reduced risk and less worry
- improved education in PAT and more satisfying conditions for employees
- improved quality of process and product
- confidence in dealing with regulatory authorities using PAT approach

Again, it is best to decide on these factors and their weight using a team based approach - the guy in charge of accounts will have a completely different idea of success compared to a process scientist. The important thing is getting to that balanced opinion.

Next, there will be a complexity in successfully implementing a project that will deliver that benefit. The following should be considered:

- cost of project
- skills available - either in house and their availability or out of house and their associated cost
- impact of this project on other initiatives and projects
- the risk of the project - Is the project a simple adaptation of a project that has been successfully implemented a hundred times before or is it completely new using cutting edge tools?
- organizational complexity - How much cross-functional involvement?

cussed in Step 1 of the Process Review

- additional information about the root cause or allied causes of the issues identified in Step 1
- issues identified by the data analysis which were not even considered by the project team

It is quite common for several issues identified in Step 1 to be discarded at this stage as projects not to take forward. This could be because sometimes myth becomes fact on the factory floor. It also could be that the issue identified is not truly the root cause, but just one of the symptoms of the underlying issue. Data analysis is extremely powerful for deciding on which projects really do exist and should be taken forward.

It is also quite common for additional issues to be identified during the data analysis step because of issues not identified in Step 1, because of a limited understanding of the process. Any additional issues, identified in the data analysis, should of course be discussed in the team to decide their relevance to the process and as to whether they should be taken to Step 3 of the Process Review.

Step 3 - Define Improvement Projects

There will always be more projects that you want to do than resources will allow. Therefore, it is important to select projects that will give you the most success for the minimal amount of effort expended on achieving it. It is also worth considering the image of PAT within the company - if the company mentality has bought into PAT, it will be possible to select some projects that indicate stellar successes even though there is a risk that a percentage of these projects may be more difficult than expected. If you are having a major battle persuading the organization that PAT is a good idea and this is your one shot to prove it, you may want to play it safe and deliver more modest, but guaranteed, PAT successes in order to spread the word that PAT does deliver advantages and is a benefit to the company.

Improvement projects can be readily defined from the outcomes of Steps 1 and 2. The problem areas based on team opinion and potential ways to solve them were defined in Step 1. Step 2 used these opinions to define what data should be analyzed. The result of this stage was either confirmation or rejection of these opinions. Data analysis will most likely have revealed other

These two opposing concerns can easily be ranked to give a simple way of prioritizing projects as shown in Figure 6, where several projects have been identified for a secondary manufacturing facility.

In this example, a team of six was used to prioritize the projects. The business benefits were calculated from the outcome of Steps 1 and 2 together with some final objective opinions gathered from the team.

The project complexity was calculated from the team who could suggest potential solutions to the problems and with it suggest the associated complexity rating. It should be possible to suggest a solution (even if it's a very broad solution such as SPC required) at this stage either by using the people in the room or using the outputs of Step 1. Figure 6 shows the outcome of this Process Review was three quick win projects (On-line SPC, Raw material ID, and on-line NIR in drying) and three longer term projects (Rapid microbial methods, line stops, and optimization of packaging lines). Four projects were rejected at this stage, because they provided too little benefit for the amount of money to be spent.

Summary

PAT has certainly been accepted by many people in the drug industry as the future, but despite this, its implementation has been at a fairly low level. Part of the barrier to this is actually the difficulty in finding those PAT projects and proving the real benefit to the business. This may be because the people suggesting such projects are thinking too locally (for example just a favored few process steps) or are favoring particular technologies or tools.

The Process Review is a way to avoid these issues and is an essential process to follow before starting PAT projects that will be beneficial to the organization and represent the best value.

First, team intelligence is used to replace individuals suggesting issues with processes. This team approach will reach an objective opinion (rather than a subjective one - no matter how good an individual expert is).

Second, this objective opinion of the process can be used to guide the data analysis stage. The purpose of the data analysis stage is to convert the objective opinion of the process into absolute facts and data. This stage will confirm some opinions, reject others, and even unearth new factual issues about the process.

The final stage is the prioritization of projects, which will overcome issues associated with the process and provide real value for money so that funds can be won in competition against other projects.

Of key importance in all of this is team work. No one expert knows everything about the process or PAT.

Acronyms

Near Infra-Red (NIR)
Process Analytical Chemistry (PAC)
Process Analytical Technology (PAT)
Principle Components Analysis (PCA)
Partial Least Squares (PLS)
Statistical Process Control (SPC)

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This case study presents how a site validation policy was developed using a modular validation approach and incorporating the latest FDA initiatives, as well as principles from ISPE's Commissioning and Qualification Baseline® Guide, GAMP® 4, and the GAMP Good Practice Guide: Validation of Laboratory Computerized Systems.

Editor's Note: In August of 2006, the Havant site validation approach was formally honored with a Wyeth Corporate Best Practice Award.

Current Good Validation Practice

by Brian Collins and Kieran Sides

Introduction

Wyth Pharmaceuticals approached Validation in Partnership Ltd. with the requirement to develop a site validation policy that would complement existing quality standards while changing the existing culture from one of multi-factory standards to one of more centralized control. The goal for this change was to present a more unified approach to regulatory compliance and respond to a number of recent and pending industry initiatives. The new policy would need to satisfy the following:

- facilitate the continuity of the focused factory management
- ensure 100% buy-in from department heads and the shop-floor
- be manageable, transparent and maintainable
- add minimum overhead
- fulfill all current regulatory requirements
- comply with the principles of ISPE's Baseline® Guide on Commissioning and Qualification¹
- embrace all foreseeable industry and regulatory trends

The 'trends' to be accommodated were those appearing in the latest guidance from the regulatory agencies and industry advisory bodies, in particular:

- the FDA's regulatory initiative: "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach"²
- the FDA's guidance on Process Analytical Technology (PAT)³
- rumors of a Quality Systems approach to inspections by the FDA⁴

It was also to later embrace:

- GAMP 4⁵ and the GAMP Good Practice Guide: Validation of Laboratory Computerized Systems⁶

More recently, there has been talk of minimizing the amount of paperwork and repeat work generated by validation departments by assigning more work to vendors and by eliminating the necessity for requalification and revalidation.

Although only needing to satisfy the requirements set down by the EMEA and PIC/S, corporate standards being issued from the USA were imposing requirements specifically designed to satisfy the FDA as well.

Overview

Up to a few years ago, Wyeth's history at its UK Havant site had been one of unparalleled commitment to the daily demands of its customer base. The name became synonymous with the epitome in fast-tracking the installation and start-up of new processes.

Inevitably, with this focus, against a background of high activity, it was realized that the level of documentation to support such new introductions would benefit from a more rigorous approach to meet the current expectations of the regulatory agencies and the company's own internal requirements.

The development of a sensible, workable, economic validation policy compliant with all current and foreseeable initiatives, and providing a springboard for the future would certainly be difficult, but not too daunting. The introduction of such a system while managing the changing routines of a pharmaceutical business with a culture of decentralized management and comprising the manufacturing and packing of a dynamic portfolio of some 250 products would, unarguably, present something of a challenge.

The answer seemed to lie in a modular validation approach designed to minimize the impact of change and the exposure of surplus information, while optimizing the level of control and ease of inspection. The solution is illustrated in Figure 1.

Please note that, while submitting this illustration, it is acknowledged that the termi-

nology applied to the activities shown differs through the industry. Similarly, it is appreciated that the division of qualification/compliance activities is handled differently between the various qualification stages from company to company. Therefore, the titles of the documents and activities referred to in this article should not be assigned any undue significance – it is their content and satisfactory completion in the correct sequence that matters.

The validation policy described is applied to all the hardware and software systems employed in a manufacturing process that are categorized as cGxP impacting, a category assigned to any system that can affect product quality. However, there are a series of crucial activities that must be formally undertaken before any such assignation is possible. They are not considered part of the validation approach, because they are not specific regulatory requirements, but without them, all ensuing validation work would be unfounded. As such, they are referred to as validation foundations.

Validation Foundations

The justification for all validation work is derived from the outcome of those activities shown in the top left hand corner of Figure 1, which comprise:

- Process and Production Rationales
- User Requirement Specifications
- Compliance Reviews
- System Definitions
- System Impact Assessments

And the deliverables determined are mapped through to provision using:

- Traceability Matrices

An expanded view of this section is shown in Figure 2.

Process and Production Rationales

The start point is a Process Rationale, which is written during process development to evaluate risks to product quality and to formally document the process critical parameters. Comprising a variety of sources, such as technology transfer documents, the Process Rationale then forms the basis of a series of risk assessments, which are performed while the User Requirement Specification(s) and the detail of the full scale production model are being developed. This iterative process is documented in a Production Rationale, which

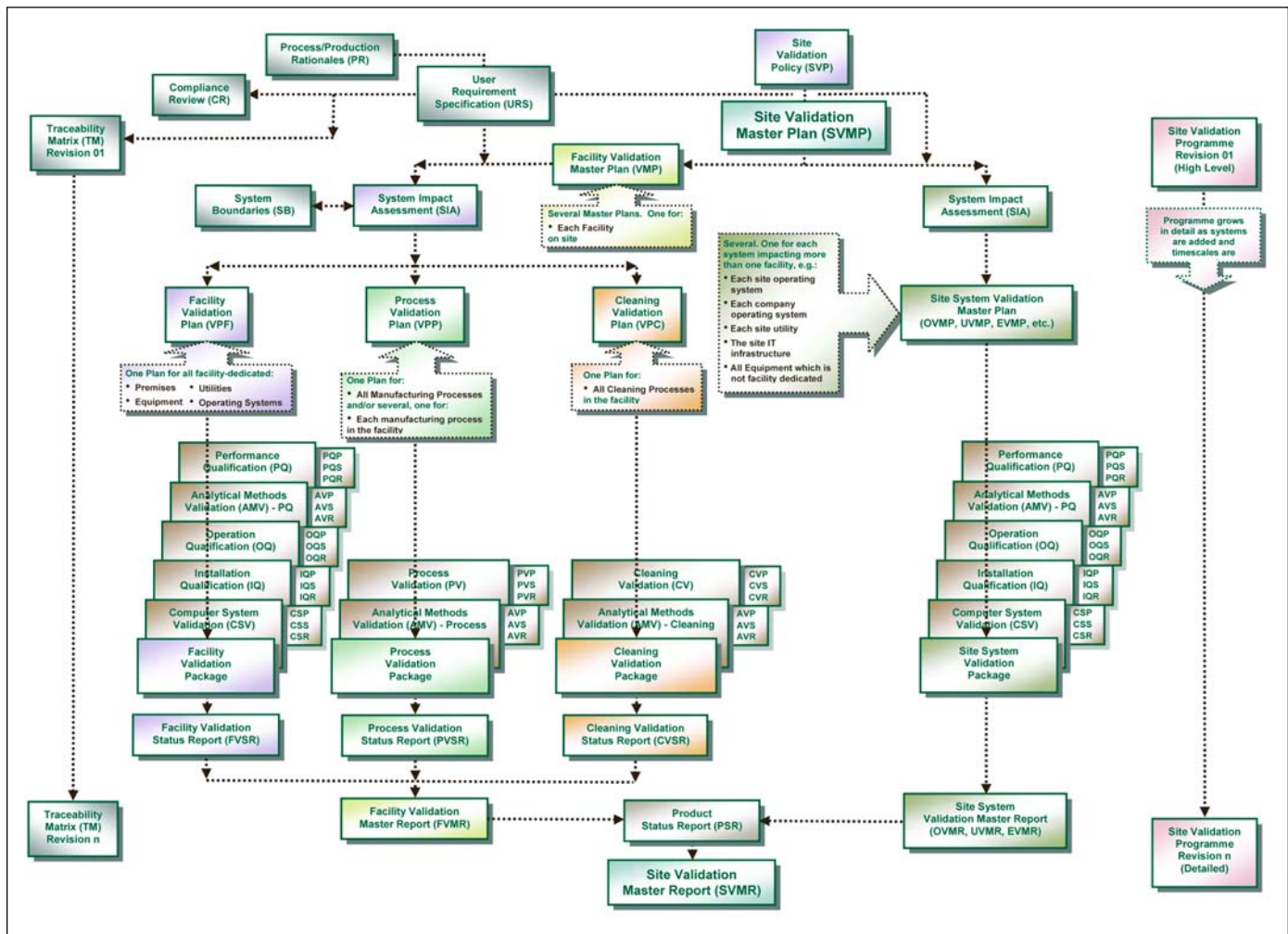


Figure 1. Validation policy overview.

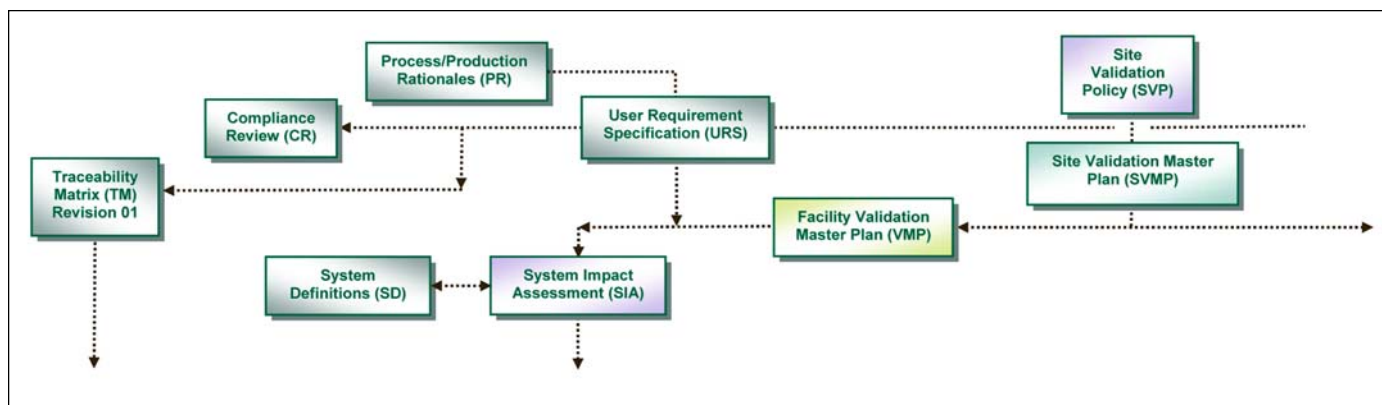


Figure 2. Validation foundations.

provides a step by step analysis of the proposed production process and a compilation of all parameters that may have an impact on the quality of the finished product. One Production Rationale can be generated for each individual product or for several products of the same type. The hardware and software process systems are the obvious focus for this, but there is a tendency to overlook other key aspects of the manufacturing process. Every step, from the arrival on site of raw materials and components, to the departure of finished product, needs to be considered. The way ingredients are specified, procured, transported, off-loaded, handled, sampled, analyzed, stored, dispensed, and charged all can have an adverse effect on quality unless properly controlled, as can in-process sampling, handling, analysis, and subsequent finished product storage and despatch.

Uninformed reactions to regulatory initiatives, such as PAT, can be counterproductive, and in certain cases, result in catastrophic failure of the quality system. Without the fundamental blueprint provided by the Process and Production Rationales, additional in-process analytical steps installed to demonstrate compliance and control may inundate the manufacturer with data providing more questions than answers. In extreme cases, this supplementary data, which cannot be ignored, has led beyond confusion and back to the drawing board, as companies have been forced to admit they did not understand their processes well enough to control them.

The finally agreed Production Rationale, which should reference all supporting development reports, provides a complete list of all product quality impacting parameters at every step, and where possible, identifies all set-points and ranges of tolerances. It is equally important that the non-critical parameters also are identified and the justification for their lack of criticality is documented. Simply omitting these from the rationale begs the question of whether they were even considered at all.

The rationale deliverable is a justification for every subsequent process control measure, whether it be by facility, utility or equipment qualification, automation validation, calibration, in-process monitoring, Standard Operating Procedure (SOP), or training. All static and dynamic attributes of the process are included. A parameter such as equipment product contact parts is assigned to Installation Qualification for verification, whereas the standing time for an off-

loaded drum of material becomes the subject of an SOP. The charging of an ingredient into a mixing vessel, if a manual operation, is controlled by approved SOP, training, and calibrated time piece, where appropriate. Dynamics such as mixing speed are covered by Operation Qualification. Thereafter, they are monitored and trended, either by a suitably independently validated and maintained automated system or by manual measurements at specified intervals by qualified individuals trained in approved SOPs and using calibrated test equipment.

If another product of similar type is later introduced for manufacture using the same process, the Production Rationale is revisited to incorporate the new product and make any necessary adjustments to the operating ranges of the process parameters.

As with all the documents referred to in this article, once approved, Production Rationales must be governed by the site change control system. System Impact Assessments will rely on these rationales to provide the parameters for qualification checking and testing, and where applicable, the ranges or operational limits.

User Requirement Specifications

The importance of the role played by User Requirement Specifications (URSs) cannot be stressed enough. They provide a home for all the known requirements of all stakeholders and are generated as a precursor to procurement of all facilities, utilities, equipment, and operating systems. The modular approach to the validation documentation system also is favored here with non-detailed Project URSs providing the master control over more detailed System URSs. Compiled as tender documents, they provide all the information necessary for prospective vendors to satisfy all the hardware, software, and documentation requirements of the Quality, Production, Engineering, and Maintenance departments. The URS covers not only the current requirements of GMP, GAMP (other GxP compliance issues, as appropriate), the registered process(es), and corporate standards, but is expanded to become a receptacle for all required deliverables.

There may be several ways in which to satisfy a particular business need so the URS is not unnecessarily restrictive. Wherever possible, designers are permitted to offer the most cost-effective and compliant solutions. In cases where there

is scope for interpretation, URSs are accepted as iterative, becoming more prescriptive as the design is developed.

There are numerous URS formats in use throughout the industry, and there are good and bad elements in all. The format adopted for the Havant site was developed with an automated documentation process in mind, which is described further on. The URS groups the requirements according to the phases of the project life cycle during which they are to be delivered with separate sections for the design, vendor assessment, construction, factory testing, installation, commissioning, operation, training and maintenance phases of the project. Each individual requirement is given a unique identifier and a suffix, the suffix denoting the origin (cGMP, GAMP, Process, HSE, etc.), e.g., “5.3 Certification exists to demonstrate that all contact part materials correspond to the approved design requirements [cGMP].” This would appear in the list of items to be verified at the Installation Phase. Each requirement is written as a clear and unambiguous deliverable that is lifted verbatim into a subsequent document as a predetermined acceptance criterion. This eliminates any later confusion arising from a misinterpretation of the requirement.

A URS is generally subject to constant development prior to procurement, but it also can be affected by changes agreed throughout the design and construction stages. With this in mind, the URS has an integrated change control mechanism to facilitate amendment. Even after the installation of a system has been qualified, there may be changes necessitated by unforeseen circumstances that will impact the URS. As all validation protocols import their acceptance criteria from the URS, the Site Change Control System ensures these modifications are captured and it is updated.

Compliance Reviews

A Request for Proposal is issued to prospective vendors and the proposed designs submitted are checked for compliance with the user requirements. This is the role played by the Compliance Review. It performs the same function as the Enhanced Design Review in the ISPE Baseline® Guide on Commissioning and Qualification,⁷ and what some refer to as Design Qualification. The EMEA suggests this ‘could’ be the first stage of validation⁷ and intimate that the compliance of the design with cGMP should be documented.⁸ The FDA, on the other hand, does not require a formal review at design stage to verify regulatory compliance, which is contradictory to the very essence of the meaning of validation.

The reason we validate is because we cannot test quality into the end product. Unfortunately, the regulators seem to have diluted this message. If we follow the letter of the law, qualification is not required until an installation is complete, which is way too late for any non-compliances to be rectified. In the real world, where projects are generally behind schedule, the discovery during Installation Qualification that the design was not all it should be, is far more likely to lead to a compromise in standards than the necessary alterations. For pure economy alone, it makes more sense to identify and eradicate potential shortcomings on the drawing board than

actual faults on site.

Each individual user requirement is verified as a deliverable of the proposed design by recording the precise location within the design package where the vendor’s intention to comply is documented. Only then can an order be placed.

It is recognized that design development is the domain of the vendor so the Site Change Control System is not invoked until the commencement of Installation Qualification. Prospective vendors are audited to verify that adequate change controls will be employed to safeguard the user requirements as the design is developed and components are procured.

Although performed at proposal submission stage, the Compliance Review incorporates a similar means of change control to the URS, ensuring that all subsequent changes to the user requirements are formally accepted by the vendor. Audits of the two change control systems at intervals prior to the commencement of Installation Qualification will confirm the vendor’s sustained commitment to compliance with the URS.

System Definitions

A System Impact Assessment will determine whether or not validation is needed, but before this can occur, the full extent of the system has to be known. A System Definition document not only identifies the physical boundaries of the system, but also provides a complete description of the static and dynamic attributes of the system. It constitutes a key ingredient of the modular approach to validation, as the descriptions in validation plans and protocols can be minimized, supported by a simple cross-reference. For something as complex as an automated Clean-in-Place system with numerous interfaces with other systems, the finished document would contain a schematic diagram, marked up to identify the start and finish points, a detailed specification of the installation and functionality, and an index identifying the references, versions, and locations of all other pertinent documentation, back-up software programs, etc. For simpler, stand-alone systems such as a refrigerator or a pH meter, a vendor’s brochure may suffice.

System Impact Assessments

With the system fully defined, the next risk assessment is performed, which is the System Impact Assessment (SIA). This is when the decision is made whether or not the system needs to be qualified. The SIA is referred to as the Impact Assessment in ISPE’s Commissioning and Qualification Baseline® Guide.⁹

The criteria provided by ISPE and the Production Rationale are used to determine if Good Engineering Practice (GEP)¹⁰ standards alone will suffice or if they need to be supplemented by the appropriate validation phases. It can be tempting to ease up on the documentation standards for systems exempt from qualification, but one day the use of a system may be changed such that it can impact on product quality and needs to be qualified. It may not be possible to qualify a system lacking the necessary supporting documentation.

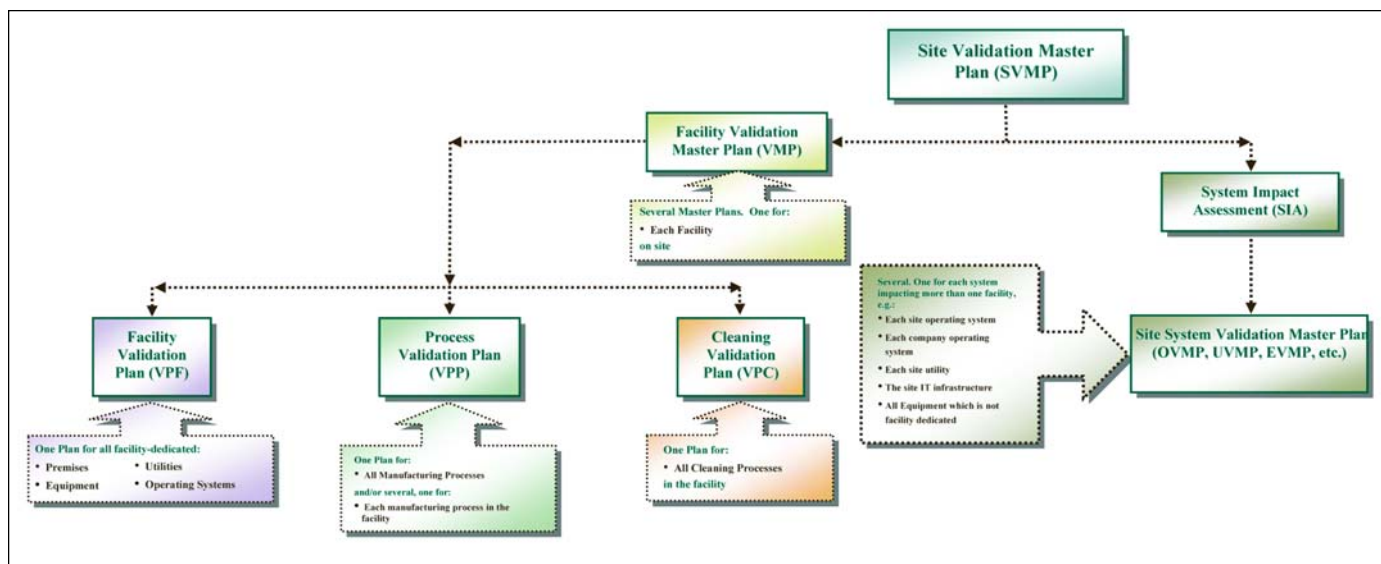


Figure 3. Validation planning overview.

Every SIA includes a matrix, which maps the system/systems covered against its/their critical parameters, as defined by the relevant Production Rationale(s). The SIA is revisited each time there is an amendment to a Production Rationale, this revisit being prompted by the Site Change Control System and its inbuilt risk assessment. For example, if the scope of an existing manufacturing process is extended to cover the introduction of an additional product, any changes required to the operational limits of any of the process parameters will be passed on to the SIA. In response to the revised SIA, the duly amended Traceability Matrix will project where an evaluation is required of the impact on the existing qualification package.

Traceability Matrices

Traceability Matrices are now in common use, plotting the projected delivery of every single user requirement to ensure nothing is overlooked. Most companies use them prospectively to define precisely where each requirement will be verified as satisfied. But they also can be used retrospectively to identify exactly where the fulfillment of a requirement is actually documented. They are used mainly to demonstrate control of the current GxP requirements, but, if the URS is properly structured, there is no reason why individual matrices should not be compiled for all other requirements, such as health, safety and environment, or corporate standards.

If more than one Traceability Matrix is generated, there also should be a master overseeing them, which, retrospectively, would verify that all individual matrices had been brought to a satisfactory conclusion.

Validation Policy

The Site Validation Policy presents the complete approach to validation across the site.

Validation Master Plans

The Site Validation Master Plan (SVMP) identifies all the types of products categorized in the site inventory as cGMP

impacting, a category that applies to all medicinal products for human use. It also lists all the individual Validation Master Plans (VMPs) generated for the site. As indicated in Figure 1, a VMP is produced for each facility on site, and for each 'site system', i.e. a system serving more than one facility (site utilities, site and company operating systems, site IT infrastructure, and equipment systems that are not facility-dedicated). The SVMP then identifies, for each product, which VMPs are impacted during any stage of its manufacturing process. An expanded view of this section is shown in Figure 3.

Validation Plans

Each Facility VMP introduces three types of Validation Plans (VPs); one for the facility, one for the manufacturing processes and products accommodated therein, and one for the associated cleaning processes. The modular approach presented here would be less beneficial to a single product facility for which it may be feasible to omit the VPs by incorporating their contents into the Facility VMP.

System descriptions in the VMPs and VPs need be nothing more than cross-references to the System Definition documents. This enables any change, other than one impacting a critical parameter, to be accommodated and documented without the need for a revision to the plan.

The Facility VP covers all the facility-dedicated systems, which include the premises (the facility itself and the various rooms) and all the equipment, utilities, and operating systems located within the facility. It acknowledges the 'site systems' serving the facility, but simply cross references to their VMPs for any detail, and it makes no mention of manufacturing or cleaning processes at all. The plan then introduces the phases of validation it controls and contains the traditional matrix plotting systems against their assigned qualification and/or validation phases. The phases covered by a Facility VP are the same as those of a 'site system' VMP, as can be seen in Figure 1.

The Process VP details the manufacturing process for each

product produced and/or packed in the facility. It groups the products in families according to their production or packing processes and identifies both the facility-dedicated systems and the 'site systems' impacting these processes. If a facility is subject to an ever-changing production schedule, it may be appropriate to modularize the approach further and generate separate Process VPs for individual manufacturing or packing processes to minimize revisions to the plan.

Although identifying all the hardware and software systems involved in each process, the Process VP merely directs the reader to the Facility VP or the 'site system' VMP for further details. It then provides an overview of the validation phases it covers, i.e., Process Validation (PV) and Analytical Methods Validation (AMV), and a matrix showing the assignment of these phases to the products and processes included in the plan.

The Cleaning VP details all possible permutations of product family campaigns for each of the production or packing processes operated within the facility and considers all opportunities of potential cross-contamination, including those involving products not categorized as cGMP impacting. The plan identifies all the equipment to be cleaned and all the systems to be used in the cleaning processes, the facility-dedicated systems, and the 'site systems.' However, it simply points to the Facility VP for further details of the facility-dedicated systems and to the appropriate VMP for each 'site system.' It also contains an introduction to the Cleaning Validation (CV) and Analytical Methods Validation (AMV) phases covered and a matrix assigning these phases against the various processes.

This modular validation planning ensures a minimization of the impact of any site changes, such as the installation of an additional compressor to increase the capacity of the Site Compressed Air System. Even though the system may serve

numerous facilities and processes across the site, the only plan requiring a revisit would be the Site Compressed Air System VMP. Similarly, the introduction of a new product, the operational limits of which are within those already tested for its product family, would require nothing more than an inventory update. There would be no need to revisit the Cleaning VP, Process VP, IQ, or OQ, and there would be no urgency to produce the three consecutive replicate batches required to validate the process; they would simply fall in line with the production schedule.

Validation Program

Annex 15 to the EU Guide¹¹ specifies that a VMP should contain data on "planning and scheduling." True to the modularity of the approach, the validation program is generated and maintained as a separate document with recognition provided by a simple cross reference from the SVMP. With a product portfolio like the one at Havant, the production schedule would otherwise render the upkeep of the SVMP impossible. A formal validation program should indicate the appropriate sequence of all validation activities covered by the VMPs and VPs, but it should always have plenty of slack built in as there is nothing more ridiculous than deviations being raised during a validation project simply because timelines have not been met. The generation of such deviations is completely pointless as they cannot possibly be resolved, merely accepted.

The program is not just a regulatory requirement, but it is also an essential validation control document. As such, all additions and removals are subjected to the Site Change Control System.

An evolutionary approach to the development of detail within the validation program as the life cycle develops is particularly important for a new or expanding site. Many

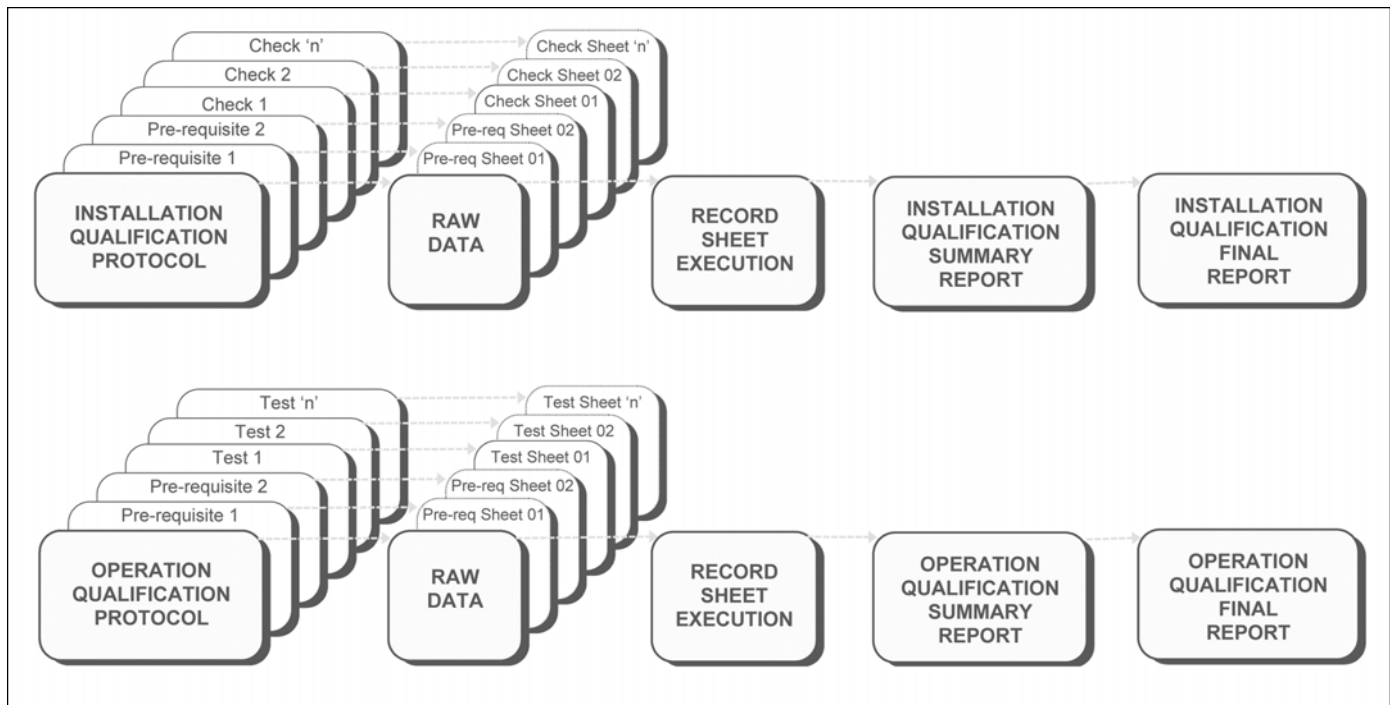


Figure 4. Qualification documentation overview.

projects have ground to a halt or been forced to proceed with unapproved or unrepresentative plans as a result of trying to define all the detail at the outset, when such detail is simply not available. This is one of the primary factors in modularizing the validation package in terms of VMPs and VPs, such that the level of detail presented in each is appropriate to the level of knowledge available at the time it is generated. A similar end point could be achieved through the continued revision of a single plan, from an initial high level approach, as represented by our Site VMP, to a detailed approach, as represented by Site System VMPs and Facility, Process, and Cleaning VPs. However, the final provision of such a plan does not lend itself to change, as even minor site modifications would necessitate the continuous revision and re-issue of what would be an extremely bulky text for approval. It is simple enough to provide a validation package to support a new site or facility, but considerably more difficult to produce a package that is easily maintainable over time.

Protocols and Reports

All protocols and reports, whether for a Compliance Review, Installation Qualification, or Process Validation follow the same modular pattern as indicated by Figure 4. Protocols are constructed such that each of the series of pre-requisites, checks and tests contained therein has its own objective, methodology, and acceptance criteria section. Each objective is to provide documented evidence that a pre-requisite has been satisfied or that a check or test has been successfully completed. The methodology sections explain only the intent and not the step by step detail of the execution procedure. This is provided elsewhere, on stand-alone record sheets. The reasons for this are several. For a complex OQ test, the heads of department nominated to approve a protocol are unlikely to be sufficiently acquainted with a system to be able to agree a detailed test procedure, but they should be comfortably qualified to approve the intent of the test.

There also may be various ways to execute a test. For instance, a test to verify the satisfactory operation of a high level switch for a purified water system storage tank can be included in the protocol with only high level detail of how this test will be conducted. For example, it will be important that a suitable quality of water is used and that the high level switch is activated when the water in the tank reaches a predefined level (with tolerance). However, it may not be necessary to charge the water from the associated purified water generation system or within a particular time period. The skill is to document the critical elements of the test methodology at a high level in the protocol, and to clearly define the supporting acceptance criteria. The detail of the valve sequences, interlocks, etc., required to safely realize the test on the plant can be derived following approval of the protocol as more detail of the installation and commissioning status of the facility becomes available.

The most appropriate way of testing might not have been decided, but this is no reason to delay what can be a lengthy protocol review and approval process. Whatever method is eventually selected, the test acceptance criteria will be the

The screenshot shows a software interface for selecting a document template. It is divided into three sections:

- Please select the type of template required:** A list of 18 items with radio buttons. The selected item is "Installation Qualification".

<input type="radio"/>	Site Validation Policy	<input type="radio"/>	Computer System Risk Assessment
<input type="radio"/>	Site Validation Master Plan	<input type="radio"/>	Computer System Design Review
<input type="radio"/>	User Requirement Specification	<input type="radio"/>	Computer System Validation
<input checked="" type="radio"/>	Traceability Matrix	<input type="radio"/>	Installation Qualification
<input type="radio"/>	Validation Master Plans	<input type="radio"/>	Operation Qualification
<input type="radio"/>	Validation Plans	<input type="radio"/>	Performance Qualification
<input type="radio"/>	Computer System Quality Plan	<input type="radio"/>	Cleaning Validation
<input type="radio"/>	Product Status Report	<input type="radio"/>	Process Validation
<input type="radio"/>	System Impact Assessment	<input type="radio"/>	Nominated Personnel File
<input type="radio"/>	Compliance Review	<input type="radio"/>	Comments Sheet
		<input type="radio"/>	Deviation Sheet
- Please select the form of the template required (as applicable):** Three radio buttons: "Protocol" (selected), "Report", and "SOP".
- Please select the subject of the template required (as applicable):** Four radio buttons: "Equipment" (selected), "Facility", "Rooms", and "Not Defined".

At the bottom right are "CANCEL" and "OK" buttons.

Figure 5. Automated document template menu.

same. When finally decided, the record sheet will prescribe the specific qualification steps to be followed in performing the test. The finished record sheet is then submitted to the most technically competent person to review the detail before approving it for execution. There is no need for a Quality department approval of the record sheet, as all the protocol approvers will see the completed sheet when reviewing and approving the report.

Separating the detail from the protocol in this way has a number of advantages, including reduced review and approval times. The most significant time (and cost) savings can be realized in respect to tests which protocol reviewers deem unnecessary or approaches with which they fundamentally disagree. In a traditional system, by this stage the protocol author would have already wasted valuable time trying to write a detailed test script, which is now redundant. In the model proposed here, such wastage is minimized.

When all the protocol record sheets have been executed and completed, a report is written to summarize their results. A Summary Report enables the next stage of validation to commence, even though there are outstanding minor deviations, and a Final Report is generated on their satisfactory resolution.

With the current emphasis on Quality Risk Management (QRM),¹² it was wholly appropriate to embrace the concept of its scientific, risk-based framework within the validation approach. Although the message of QRM, and particularly PAT, is often focused on in-process control and analysis, the principles should be spread to cover any part of the process where enhancements can increase product quality.

Since 1987, the FDA's Guideline on General Principles of Process Validation¹³ has stated "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics." It was decided that QRM should now be applied, not just to the consistent production of product, but also to the production of the documented evidence. To this

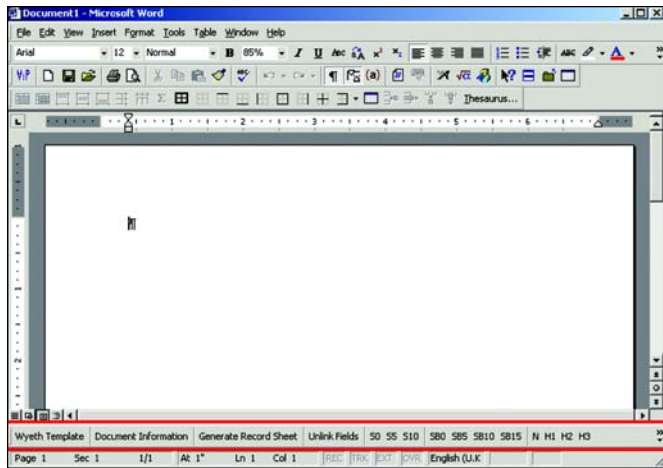


Figure 6. Automated document template toolbar.

end, the entire documentation process illustrated in Figure 1 was automated to minimize the risk of human error, an ever present feature of paperwork systems.

Automated Document Templates

Microsoft Word templates were developed initially for all the validation documents to instantly generate Validation Master Plans and Reports, Validation Plans and Reports, Installation, Operation, and Performance Qualification (IQ, OQ, and PQ) Protocols, Computer System, Cleaning Validation, and Process Validation (CSV, CV, and PV) Protocols, and Record Sheets and Reports.

The scope was then broadened to provide automated templates for the validation foundation documents, such as User Requirement Specifications, Traceability Matrices, System Impact Assessments, and Compliance Reviews. Finally, Computer System Validation (CSV) support documents, such as Quality Plans, Risk Assessments, Design Reviews, and Configuration Reviews also were automated, providing templates for both GAMP's System Development and System Implementation Life Cycles. These refer to the requirements

DOCUMENT INFORMATION	
Document Type:	PROTOCOL
Main Document Title:	[INSERT TITLE]
Header Title:	[Insert System Name]
Issue Date:	21 November 2005
Authors Name:	[Insert Name]
Authors Job Title:	[Insert Job Title]
Document Ref:	[INSERT REF.]
Revision:	[xx]
System Name:	[Insert System Name]
Validation Plan Ref:	[INSERT REF.] Rev. [xx]
Company Name:	Wyeth Pharmaceuticals
<input type="button" value="CANCEL"/> <input type="button" value="OK"/>	

Figure 7. Document information prompt table.

specified in GAMP 4 Guide to Validation of Automated Systems and the more recent GAMP Good Practice Guide: Validation of Laboratory Computerized Systems respectively.

To create a document, the author simply selects the type of template required from a menu, similar to the example shown in Figure 5, and accessed via the purpose designed toolbar shown in Figure 6.

The selection of Installation Qualification prompts the author to choose between the Protocol or Report forms of the template and the subject matter, Facility, Rooms, or Equipment. The menu display changes depending on the type of template selected. For instance, a document of the chosen type, such as an Equipment System Installation Qualification (IQ) Protocol, instantly appears when selected. Selection of the Document Information button on the toolbar enables its personalization as the author is prompted to input the specific details requested in Figure 7.

This information is then automatically fed onto the document front approval page, into the header, and consistently throughout the document, wherever necessary. The templates contain as much boilerplate text as possible with the author only having to provide details of the system description, drawing, equipment and instrumentation specifics. The Equipment System IQ template is used for utility and equipment systems with separate templates provided for facilities and rooms. The IQ and OQ elements of computer systems are built into the Computer System Validation Protocol itself.

Rather than the author having to decide on the regulatory compliance criteria for IQ protocols, each template already contains all the acceptance criteria required to satisfy the FDA and EMEA. These are grouped under logical headings and the author merely deletes those not applicable. These acceptance criteria are provided courtesy of Validation in Partnership's in-house regulatory database, which affords immediate access to all the regulatory requirements of the FDA and EMEA.

Once the IQ Protocol is generated, its system-specific Objectives, Methodologies, and Acceptance Criteria for all the pre-requisites and checks to be executed during the qualification are each translated into stand-alone Pre-requisite Sheets and Check Sheets, also at the touch of a button - Figure 4. Each record sheet carries all the necessary Document Information from the protocol. Requiring only one pre-approval signature, the record sheets are ready for execution. They carry the exact wording of the objective and acceptance criteria, as extracted from the protocol, and the prescriptive step by step instructions on how to complete the tasks. The automation ensures there can be no possibility of the all too common transcription errors from protocol to record sheet or vice versa.

Once the record sheets have been field-executed, the reports are equally instantaneously generated via the menu. The author is presented with a report prompting the appropriate choice from all necessary options. The report is generated as either an Equipment System Installation Qualification **Summary** Report (IQS) in the case of minor outstanding deviations, or a **Final** Report (IQR) if they have been resolved.

Traceability

An evolving appreciation of the possibilities for the automated templates led to the cementing of the entire validation approach. Individual user requirements are now automatically lifted into the downstream documents that are used to verify their delivery. All items listed in the Installation Phase section of a URS, that are destined for verification during validation, find themselves automatically transported into the acceptance criteria section of the appropriate check in an IQ Protocol. Those in the Operation Phase likewise become acceptance criteria in OQ Protocols. The example given above under **User Requirement Specifications** would become IQ acceptance criterion “*Certification exists to demonstrate that all contact part materials correspond to the approved design requirements [CGMP]. [URS Ref. 5.3],*” automatically maintaining the precise wording and its unique URS reference. Those not requiring verification via the validation documentation system can be automatically transported into equivalent Good Engineering Practice system documents.

The requirements recorded in the various project life cycle phases of a URS are automatically lifted into:

- Compliance Review Protocol templates and beyond into executable record sheets
- Traceability Matrices to project the documented evidence of the delivery of each individual user requirement
- IQ templates and record sheets
- OQ templates and record sheets
- PQ templates and record sheets
- Process Validation templates and record sheets
- Cleaning Validation templates and record sheets

Further enhancements will see requirements being lifted into Factory Acceptance Testing and System Acceptance Testing templates.

The entire system of documentation comprising the template menu in Figure 5 is fully supported by SOPs, which include examples of all document types and also personnel training/assessment sections.

Validation Maintenance

As is too often the case, especially when using an outside contracting organization, a manufacturing facility is completed and the qualified package is inadequately handed over to the user. By this stage, timescales are so tight that nobody has noticed. The contractors are looking toward their next project and the user is desperate to complete the process validation work and start filling the shelves with product.

Operators are trained in approved production and cleaning SOPs; the analytical methods are validated; QC personnel, schooled in sampling techniques, are waiting in the wings; the validation documentation is safely in the hands of the Quality department and the project support information is tucked away with Engineering and Maintenance who are wading through the mountain of instruction manuals and putting the finishing touches to the maintenance and calibration SOPs. All that stands between where we are now and

routine production are the process and cleaning validation stages. All that stands between where we are now and the slippery slope to non-compliance, that is.

Most of us are so glad to get through to the process validation stage relatively unscathed that one major interface is overlooked. Maintenance personnel have absolutely no idea what part they have to play in the upkeep of the facility’s validated state, because nobody has thought to tell them. They know precisely what to do to keep the process systems up and running, because the system vendors have imparted all this knowledge. But what about the flow velocity in the purified water system? Unless instructed to ensure the same critical parameter requirements tested and verified at OQ are retested and reverified following maintenance, the system will be subjected to only the vendors recommended checks and a steady drift into non-compliance is inevitable.

This is yet one more reason for keeping record sheets separate to protocols to enable the maintenance of the qualified or validated state of a system. Agreement reached by the appropriate involvement at the validation stage can lead to the Maintenance department providing the necessary assurance. Instructed in which IQ checks and OQ tests need to be performed in response to preventive or breakdown maintenance, copies of the corresponding approved blank record sheets can be executed and completed by maintenance personnel as a matter of routine. This documentation, combined with data generated during trending of critical parameters will provide the necessary justification for not requalifying or revalidating the system. Unless results determine otherwise, all that is required is an occasional audit. With record sheets completed by Maintenance filed with the originals completed by Validation, the history of a particular test and the current state of validation can be effectively demonstrated.

Three monthly summary reports of critical parameter trending following OQ, combined with the upkeep assured by Maintenance and the Site Change Control System, provide an invaluable and readily available source of input into Annual Product Reviews.

Engineering Files

Traditionally, there has been a tendency to keep project documentation referred to during IQ and OQ with the validation documents themselves to ensure they can be retrieved during an audit, but with the appropriate controls in place, this need not happen. The Engineering department should be the home for all documentation provided by system vendors. With appropriately structured system files, there should be no need for any of it to reside in the Quality department. Secure in the knowledge that strict documentation control systems are exercised, IQ, OQ, and CSV protocols should merely refer to the locations and references of supporting documentation.

Summary

The response to the remit set for the site validation policy has resulted in a living system that has fulfilled all criteria and evolved into an economical, manageable, auditable, and

maintainable validation system that has won corporate recognition and been praised during recent regulatory authority audits.

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About the Authors




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Kieran Sides has more than 16 years of experience in the qualification and validation of facilities, utilities, equipment, and systems associated with the life science industries, mainly pharmaceuticals. For the last 10 years, he has been a compliance consultant with Validation in Partnership Limited, a specialist validation and GxP compliance service provider based in the UK, during which time he has spent three years as the course tutor for the validation module of Manchester University's Pharmaceutical Engineering Advanced Training (PEAT) Programme. Sides can be contacted by telephone at +44 (0)1625 572777 or by email at: Kieran.sides@vipltd.co.uk.

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This article describes a process that was developed and successfully used to directly solicit and capture the opinions and insight of individuals in the pharmaceutical industry in a format that could assist a university with development of a new graduate program.

Implementing Industry Focus Groups to Identify Skills and Knowledge Expectations for Recent College Graduates

by Jon Tomson, John E. Connors, and Matthew A. Wells

Introduction

Since 2004, the International Society for Pharmaceutical Engineering (ISPE) has sharpened its focus on developing relationships with academic institutions and promoting stronger linkages between academia and the pharmaceutical industry. With the development of its new strategic plan earlier this year, the Society recognized that these linkages are crucial to its vision to spur innovation in pharmaceutical manufacturing sciences and technology. ISPE initiated the Pharmaceutical Manufacturing Professional of the Future program to identify the core elements of knowledge needed by new professionals entering the pharmaceutical workforce in order to function effectively in the industry's team environments. The focus group process is an essential step in this program. Our intent is to work with leading academic institutions around the globe to integrate this knowledge base into baccalaureate and graduate level degree programs supporting both new professionals and those currently serving the industry.

The Society hopes that this process can serve as a model that can be adapted for use by other companies and universities as a part of the curricular review process for an established program or in the development of new academic programs and/or courses.

Background

Pharmaceutical companies spend significant time and expense training new employees, especially recent college graduates, to bring them

up to speed as fully contributing team members. This investment occurs in every organization and across all functional areas of the enterprise - from development to manufacturing, engineering, supply chain, and compliance. In addition, some companies incur significant losses each year as a result of inadequate or insufficient training.

In 2005, representatives from AstraZeneca and Philadelphia College of Pharmacy at University of the Sciences in Philadelphia met to discuss how the university could assist AstraZeneca in significantly reducing the time it takes recent graduates to become fully functioning members of their teams. ISPE also was invited to participate in this discussion. Representatives of Philadelphia College of Pharmacy believed that the initial step in approaching this challenge was to fully understand the company's expectations for the skills and baseline knowledge of new employees and the types of training that were being provided. ISPE identified this as an opportunity to assist both parties while furthering the Society's vision in at least three areas:

- encouraging and sustaining University-Industry partnerships
- providing input into the preparatory experiences of graduate and undergraduate students who were destined for careers in the pharmaceutical industry
- extending consideration beyond the industry's current needs toward substantive discussion of the Pharmaceutical Manufacturing Professional of the Future and the

emerging requirements of science and responding manufacturing technologies

Developing the Model Process

A three person working group with representatives from ISPE, AstraZeneca, and Philadelphia College of Pharmacy was formed to develop a mechanism to identify AstraZeneca's expectations for the baseline knowledge and skills of the new college graduates that were being hired. A variety of mechanisms were considered for this purpose, including the use of paper- and internet-based survey instruments, individual interviews, and focus groups. A decision was made to utilize focus groups for this purpose because of the complexity of the topics, the degree of detail that was desired, the opportunity to clarify uncertainties in respondent's comments and ask follow-up questions, and to take advantage of the synergies that frequently develop in group activities.

To yield information that would be useful for curriculum development and design, the decision was made to address the following three general areas in the focus groups:

- What is the gap between the knowledge and skills that the hiring manager expects a new employee to bring to the job and the actual knowledge and skill set the new employee is observed to possess?
- What knowledge and skills does a new employee need to possess or acquire to be successful in their company?
- What attributes define an employee who makes a significant difference and is upwardly mobile within your company?

To ensure coverage of a broad range of subjects in the focus groups, topics were grouped into knowledge domains. Meetings were held involving representatives of Philadelphia College of Pharmacy, AstraZeneca, and ISPE to identify a set of knowledge domains that would be inclusive of the specific knowledge areas and skills that participants

were likely to identify in the focus groups. The subjects considered ranged from disciplines such as pharmaceutical sciences and pharmaceuticals to chemical engineering. The result was a set of knowledge domains that was not specifically tied to any one academic program area, but rather encompassed a broad range of subject areas. This strategy was adopted with the belief that it would enable the focus groups to delve into each domain to whatever depth and from whatever perspective participants deemed to be important. A second reason for not aligning the domains with a specific academic discipline was to encourage focus group participants to view the exercise from a multidisciplinary perspective. This was thought to be consistent with the way in which the pharmaceutical industry draws upon several different professional disciplines to create operational teams in areas as diverse as compliance, development, manufacturing, and supply chain management to name a few. The hope was that this tact would not overtly steer a focus group's deliberations to concentrate on only one or two disciplines.

Focus group participants were asked to identify the personal attributes of individuals that were very successful within their company. Attributes in this context were defined as traits, rather than specific knowledge or technical skills. As such, they are interpersonal and behavioral in nature, and they are often referred to as "soft skills." Examples of these attributes include working in teams, negotiating skills, entrepreneurial spirit, creating consensus, writing skills, and oral presentation skills.

Logistical Considerations in Organizing and Running the Focus Groups

Assumptions and General Parameters

- The size of each focus group was generally limited to 12 participants to ensure that each could actively participate in the discussion.
- Each focus group was to include representation from a broad cross section of functional areas so as not

to skew results in any one particular direction.

- The entire focus group process, including the introduction and conclusion/summary, must not exceed three hours in length.
- Each participant was to receive a written explanation of the purpose of the project, the subject for discussion, and the desired outcomes prior to attending the session.
- Each participant was also to receive information about evolving trends in pharmaceutical manufacturing to stimulate their thinking prior to the session.
- Focus groups were to be brainstorming sessions without preconceptions and predetermined findings.
- The focus group sessions were designed to be stimulating and enjoyable for the participants.
- As a reference for curriculum developers at Philadelphia College of Pharmacy, an audio recording was made of each focus group session. Participants were notified of this near the start of the focus group session, and they were informed that no comment(s) would be attributed to a specific individual.

Selection of Focus Group Participants

The decision was made to run three focus groups. When selecting focus group participants, consideration was given to their operational area(s), hierarchy within the company, and employer.

Each focus group included industry professionals who had specific responsibilities in a broad range of operational areas. At a minimum, each focus group included participants from the following functional areas:

- Development
- Manufacturing
- Engineering
- Supply Chain
- Regulatory Compliance
- Supervisory Management

There was an interest in including persons representing the full range of hierarchies within the pharmaceutical

industry, from line managers to directors to vice presidents in the focus groups. The participants in Focus Group One were all senior managers. Focus Group Two was comprised of directors and line managers and professionals. Focus Group Three was a blended group representing the full range of hierarchical positions.

As a partner in this process, we were fortunate to have AstraZeneca provide a significant number of their employees to participate in Focus Groups One and Two. Focus Group Three had representation from a cross section of pharmaceutical companies in the tri-state region of Delaware, New Jersey, and Pennsylvania, including Bristol-Myers Squibb, Cephalon, GlaxoSmithKline, IPS Process and Technology, Johnson & Johnson, Merck, and Wyeth.

Running the Focus Group Sessions

The ISPE representative served as the facilitator for all three focus groups. Following a welcome to participants, participant introductions, and overview of the process, each session began with the facilitator posing a gap analysis question:

“When you hire new people to work in your respective areas, you often need to provide orientation and training to bring them up to speed so that they can contribute as full members of your teams. For the recent college graduates you hired (undergraduate and graduate level), what were the primary gaps that you found that had to be addressed through training, mentoring, or other means?”

The facilitator then led the entire group through a brainstorming session. Participant input was captured on flipcharts. Once each of the participants had contributed to the gap analysis, all items were reviewed for clarity of meaning. In reflecting on the process used in Focus Group One, it was recognized that the items identified in the gap analysis needed to be placed in perspective. Therefore, in Focus Group

Two and Focus Group Three, each participant was asked to identify the three items that they believed were the most important or most often required attention. The items in the gap analysis were then prioritized based on the number of aggregate votes each received.

Following the gap analysis, the group was presented with the list of the seven knowledge domains, and each domain was defined in general. The facilitator led the entire group through a brainstorming session on the “Compliance and Quality” domain in order to model the process that would be utilized for each of the six remaining domains. As with the gap analysis above, one question was posed by the facilitator to begin the process and participant input was recorded on flipcharts:

“For this knowledge domain, there are several areas of specific understanding, baseline knowledge, or specific subject matter expertise that together would enable a person to effectively bring this knowledge to bear on challenges and responsibilities that might arise on the job. What are the subject matter areas that underpin the “Compliance and Quality” knowledge domain from your individual perspective?”

Prior to the start of the focus group session, each participant was assigned to one of three roundtables. The strategy in making the roundtable assignments was to make the membership of each roundtable as diverse as possible with respect to functional area and hierarchy. Once brainstorming for the “Compliance and Quality” knowledge domain was complete, participants broke into their preassigned roundtables. Each roundtable was given a flipchart and assigned to brainstorm subject matter for two of the remaining six knowledge domains. Approximately one hour was allocated to complete this activity.

Each roundtable reported and explained their list of subjects for each knowledge domain to the entire group. After each presentation, participants

were given the opportunity to ask questions for clarifications and to add subjects to the list for each knowledge domain. The facilitator then worked with the entire group to reduce duplication by combining like items within each knowledge domain. For each knowledge domain, participants were then asked to carefully review the list of subjects and to individually identify what they thought were the three most critical subjects/items for new employees to know or be able to perform. Participants were then given stickers and asked to place one sticker next to each of their critical subjects/items where they were originally recorded on the flipchart pages (3 stickers/knowledge domain \times 7 domains = 21 stickers/participant). This provided a visual representation of the relative importance that the group placed on subjects/items within each knowledge domain. The facilitator then asked the group if there were any surprises in the results and led a brief discussion regarding their general observations about the results.

It should be noted that following Focus Group One, there were refinements made to the process for using the stickers to identify the relative importance of subjects/items within each knowledge domain. In an attempt to limit bias while participants were placing their stickers on the flipchart pages, they first wrote their three selections for each knowledge domain on a data collection sheet. Participants then used their data collection sheet as a reference as they placed their stickers on the flipchart pages.

The final substantive activity of the focus group session was to identify the personal attributes of individuals that were very successful within their companies. Approximately 30 minutes was allocated to this activity. To engage the focus group participants in identifying these attributes, the facilitator posed the following question:

“Each of you works with certain people who you consider to be best-in-class. These are the people who you are pleased to see assigned to a task team that you are involved

CPIP™ Areas of Knowledge	Focus Group Knowledge Domains
Product Development	Development
Quality Systems	Compliance and Quality
Regulatory Compliance	
Production Systems	Manufacturing
Facilities and Equipment	Engineering
Supply Chain Management	Supply Chain
	Business Management
Information Systems	
	Biological/Chemical Sciences

Table A. Comparison of knowledge areas between CPIP™ and focus groups.

with or are in a meeting with you to resolve a critical issue. They may or may not be technical experts. Often, there is something other than technical expertise that causes people to listen intently to them, to look up to them, to aspire to be like them. Think of your job and your company and identify these people in your mind. What are the traits that they bring to their work?"

The participants' insights and observations were again recorded on flipcharts by the facilitator. The facilitator then provided thoughts regarding how each person could begin to work on these attributes for their own professional development.

Each session concluded with a discussion of both what worked and what needed to be improved in the process.

An agenda – flow diagram for a typical focus group session is provided in Appendix A.

Analysis and Discussion

Participants viewed the industry focus group process as a positive experience, and there was broad consensus that the pharmaceutical industry needs to better define and communicate its needs and expectations to colleges and universities. Participant input into the process led to process changes and improvements in subsequent focus group sessions. The one constant was the construct of the facilitator questions and use of the same list of knowledge domains.

In developing the model, described here, there was recognition that there is no one correct answer regarding the

base knowledge, skills, and attributes that a new hire brings to the job or acquires via the orientation process and on the job training. ISPE's interest was first to determine whether the industry focus group approach was a timely and realistic method through which we could begin to identify industry workforce needs and requirements. Beyond this, the Society wants to establish and document a process that yields information that can be utilized by colleges and universities as a part of their evaluation and assessment activities for existing curricula or in the design of new programs. Such eventual use of focus group results will be the true indicator of the value of the focus group process to industry as time passes.

Based on feedback from Philadelphia College of Pharmacy, the focus group process appears to be an effective method to gather industry perspectives and insights on the knowledge, skills, and attributes that they value in their employees, including new recruits. The consideration of functional areas in assigning participants to roundtables appears to have been effective in bringing a multidisciplinary perspective to the roundtables' deliberations although no effort was made to directly measure the effectiveness of this approach. Although the inclusion of senior management, middle management, and line professionals in focus groups provided a diversity of opinions, it is unclear if senior managers and middle managers/line professionals need to be in separate focus groups to achieve this result or if all three levels of personnel can be combined in the same focus group.

By their very nature, focus groups

represent the thinking and perspective of only a very small number of industry professionals. Therefore, caution must be exercised in using focus group results for making strategic decisions. Although an important source of information, focus group results should be used in concert with other information in making strategic decisions. Accordingly, this article focuses on the process rather than the focus group findings. Selected focus group findings are presented in Appendix B.

As the information base expands to other areas and focus groups, the information available will be more comprehensive and indicative of industry's viewpoint regarding their expectations regarding the workforce and their educational preparation.

Since 2004, ISPE's Professional Certification Commission, a broad group of industry and academic professionals, has been developing a global program for certification of professionals working in the pharmaceutical industry (see "Developing and Implementing a Certification Program to Drive Change in the Pharmaceutical Industry," Jerry Roth, Dr. Russ Somma, Dr. Sandra Greenberg, and Alexander Demos, A Supplement to *Pharmaceutical Engineering*, May/June 2006 – Volume 26, Number 3). An essential part of the development work for creating the basis for the Certified Pharmaceutical Industry Professional™ (CPIP™) was identification of critical areas of knowledge that should define an industry professional. There is speculation that if the CPIP™ areas of knowledge were incorporated into academic curricula, graduates could leverage part of their academic coursework in fulfillment of some certification requirements.

Table A identifies both the CPIP™ areas of knowledge and the knowledge domains probed in the model focus group process. The intention of the focus group process was not to be prescriptive or directive, but rather to utilize the brainstorming and prioritization activities to determine what core subjects comprise each knowledge domain. Table A illustrates that the breadth of the focus group knowledge

domains is inclusive of most of the CPIP™ areas of knowledge. For example, the focus group “Compliance and Quality” knowledge domain may encompass both the “Quality Systems” and “Regulatory Compliance” CPIP™ areas of knowledge. However, an item by item comparison would need to be performed to evaluate this relationship. No consideration is being given to aligning the focus group knowledge domains with the CPIP™ areas of knowledge and competencies required for certification as defined by ISPE’s Professional Certification Commission.

Future considerations for refinement and use of the focus group process include the following:

1. An additional focus group(s) comprised of recent graduates (BChemE, MS, PhD, etc.) with fewer than three years of pharmaceutical industry experience would create a strong comparative information set.
2. The focus groups run to-date come from one geographic area which has its unique composition of industry employers. Additional focus groups from other geographic areas with different compositions of industry employers such as start-up enterprises, biopharmaceuticals, and generics may have different results. Focus groups conducted in other countries or on other continents also may yield different results.
3. Future focus groups could be designed to provide information relevant to a specific type of degree program.
4. ISPE would like to make the results of these and future focus groups conducted on a variety of subjects and in various populations accessible to academic program planners and curriculum committees via the ISPE website.
5. Finally, a stronger futuristic view needs to be built into the focus group process. It is certainly useful to identify industry needs, preferences and expectations for employees to be recruited in the next few years. With the scale of changes in global business models, regulatory compliance processes, and the science and technology used to drive both development and manufacturing, there is a need to identify the attributes and knowledge that the industry will demand of its employees five to 10 years out.

Summary

In the near term, the results of this initial work will be utilized by Philadelphia College of Pharmacy at University of the Sciences in Philadelphia to develop a new Master of Science degree program. In the future, the basic focus group process described here can be used to gather information that can hopefully be placed in the public

Focus Group One	Focus Group Two*	Focus Group Three*
Facilitating Teamwork	Project Management Skills	Communication (Technical writing)
Time Management	Six Sigma	Leadership skills
Writing Skills for FDA	Regulatory/GMP	Compliance Requirements
Negotiation Skills	Molecule to Medicine	Regulatory 101
Product Life Cycle	Presentation Skills	Teaming Skills
Change Management	Good Engineering Practices	Basics of Drug Development
Ability to see the Big Picture	Teaming/Management	Hands-on Knowledge
Experience (Internships)	Technical Writing	Statistical/Experimental Design
Strategic Decision Making	Communication (Listening)	Formulation, Scale-up 101
Formulations	Application Theory to Specification Root Cause	Strategic Decision Making
Understanding Financials	<i>Time Management/Multitasking</i>	<i>Time Management</i>
Understanding the Organization	<i>Ops Research/Organizations</i>	<i>Understanding Global Business</i>
International Regulatory View	<i>General Industry Understanding</i>	<i>Process Control/SPC</i>
IT Best Practices	<i>Data Mining</i>	<i>Numerical/Process Modeling</i>
Risk Management	<i>Safety, Health, Environmental</i>	<i>Crystal Isolation</i>
Supply Chain Interdependency	<i>Conflict Resolution</i>	<i>Conflict Resolution</i>
Packaging/Distribution	<i>Packaging Sciences</i>	<i>Packaging Sciences</i>
Understanding Global Business	<i>Lean Sigma</i>	<i>Lean Sigma/Risk Management</i>
Presentation Skills	<i>Change Management</i>	<i>Presentation Skills</i>
Working Virtually	<i>Good Equipment Practices</i>	<i>Financials</i>
Individual Attitude (Smile)	<i>Financials</i>	<i>Project Management</i>
	<i>SPC/Design of Experiments</i>	<i>ICH Global Compliance</i>
	<i>Contract Law</i>	
	<i>Basic Automation</i>	
	<i>Analytical Chemistry/Testing</i>	
	<i>Understanding Cultural Differences</i>	
	<i>How to Develop an Idea</i>	

*In descending order of priority, gaps in red either one or no votes

Table B. Gaps identified by focus groups.

Focus Group One	Focus Group Two	Focus Group Three
Good Manufacturing Processes (7)	GMPs (7)	GMPs and International (8)
Current and Risk-based Validation (7)	Risk Management (4)	Quality Systems (8)
Ethics (5)	International Regulations (3)	Fundamentals of Validation (6)
Financial Compliance (3)	Validation and Qualification (2)	Quality by Design (3)
Practical Applications within Industry (2)	Quality/Compliance (2)	Working in a Regulated Industry (2)

Table C. Priority subjects within Compliance Knowledge Domain.

Focus Group One	Focus Group Two	Focus Group Three
Process Robustness (6)	Drug Development (7)	Molecule to Market (10)
Manufacturability (6)	Formulation (5)	Quality by Design (8)
Particle Technology (4)	Process Analytical Technology (5)	Technology Transfer (8)
Product Design (4)	Scale-up (3)	Biopharmaceutics (6)
Technology Transfer (2)	Technology Transfer (3)	Statistical Process Control (2)

Table D. Priority subjects within Development Knowledge Domain.

Focus Group One	Focus Group Two	Focus Group Three
Process Analytical Technology (7)	Manufacturing Technologies (8)	Process Troubleshooting (7)
Emerging Technologies (6)	Forms (6)	Materials Management (6)
Process Optimization/Packaging (5)	Leadership People Skills (5)	Facility Design and Utilities (6)
Lean Manufacturing (2)	Technology Transfer (2)	Six Sigma Lean Manufacturing (5)
People Skills (2)	Labor Relations (2)	Unit Operations (4)

Table E. Priority subjects for Manufacturing Knowledge Domain.

Focus Group One	Focus Group Two	Focus Group Three
Outsourcing Third Party Relationships (8)	Strategic Planning (8)	Global Business Practices (7)
Product Understanding (6)	Lean and Six Sigma Practices (5)	Network Strategies (7)
Enterprise Resource Planning Systems (4)	Global Marketing (5)	Lean Sigma (5)
Lean Sigma (4)	Operational Research (4)	Logistics (5)
Global Supply Chain Dynamics (4)	Supplier Quality Measurement (3)	Outsourcing (4)

Table F. Priority subjects for Supply Chain Knowledge Domain.

Focus Group One	Focus Group Two	Focus Group Three
Automation (8)	Aseptic Processing (8)	Pharmacology/Pharmacokinetics (7)
Control Parameters (7)	Containment and Isolation (5)	Design of Experiments (7)
Small vs. Large Molecule (7)	Purification and Separation (4)	Particle Sciences (5)
Sterilization and Cleaning (5)	Safety and Environmental (3)	Analytical Techniques (4)
Process Design and Science (1)	Process Design and Control (3)	Microbiology/bio-burden (3)

Table G. Priority subjects for Science Knowledge Domain.

domain so that colleges and universities will have a tool to gauge the focus of both current and anticipated offerings that are devoted to preparing students for careers in the pharmaceutical industry.

Appendix A - Flow Diagram for a Typical Focus Group Session

Supplies Needed for the Focus Group Sessions

- at least three flipcharts
- tape to attach flipchart pages to the wall (if pages do not have self-adhesive)

sive)

- colored markers for flipcharts
- stickers (multicolored half-inch diameter dots were used here)
- list of knowledge domains

Activities to be Completed Prior to the Scheduled Date of the Focus Group

- Send participants a written explanation of the focus group process.
- Send participants a brief article to stimulate their thinking.
- Assign participants to roundtables.

Focus Group Process:

Introduction (15 minutes)

- welcome to participants
- self introduction of all participants
- overview of the focus group process

Gap Analysis (25 minutes)

- context for identifying gaps
- provide the gap question
- brainstorm gap ideas
- prioritize gaps

Brainstorming Session for the First Knowledge Domain (15 minutes)

- context for knowledge domains
- full group brainstorming on Compliance Domain

Brainstorming Roundtables for Remaining Six Knowledge Domains (50 minutes)

- assign breakout groupings and two domains per group.
- encourage a minimum of ten subjects identified for each domain
- breakout groups to determine spokesperson to report findings

Coffee Break (15 minutes)

Breakout Group Reports and Additional Brainstorming (20 minutes)

- each spokesperson reports results
- full focus group challenges results to identify areas of duplication and convergence and note any other subjects not identified for each domain

Prioritization and Voting (20 minutes)

- Facilitator reviews all results.
- Participants vote on their choice for the top three subjects comprising each knowledge domain.
- Once all have completed their ballots, participants use dots on charts to indicate their selected subjects.
- Votes are counted and priority subject areas are confirmed and reported out to focus group.

Brainstorming on Attributes of Successful Employees (20 minutes)

Conclusion (10 minutes)

- Thank participants for their time and insights.
- follow-up or next steps, if any
- concluding remarks

Focus Group Duration: 3 hours, 10 minutes

Appendix B - Selected Focus Group Results

Gap Analysis

Table B provides the results of the gap analysis for the three focus groups. Note that Focus Group One did not prioritize the gaps that they identified.

Review of the gaps identifies several areas of convergence. In the two focus groups that developed a prioritization there were three areas that were strongly related, both across the priorities and in the results. Focus Group One: Communication including Technical Writing, Regulatory Compliance, Teaming Skills, and the Basics of Drug Development and Manufacturing Processes. Interactive skill gaps also are identified across the three focus groups included: Presentation Skills, Conflict Resolution, and Negotiation Skills. Organizational skill gaps include: Understanding of the Global Business, Understanding Financials, Change Management, and Time Management. Other gaps showing convergence among the focus groups are: Packaging, Risk Management, and Supply Chain. It is interesting to note that gaps in areas related to emerging science and technology focused on manufacturing were cited by some groups, including: SPC and Design of Experiments, Lean Sigma, Process Control, and Risk Management. Areas that were not brought out by the focus groups also related to science based manufacturing that might be considered for some programs include: Closed Loop Process Control, Solid to Solid Interactions, Process Understanding and Control, and Understanding of Particle Size Reduction Techniques.

In summary, there are multiple areas where our focus groups thought gaps exist and where they or their companies often have to intervene to bring new employees up to speed. Some of these gaps might be dealt with through survey and introductory courses, while others are very detailed and subject specific. There are also gaps seen in the areas involving softer skills and interaction among teams and people, many of these areas may be addressed via exercises and assign-

Focus Group One	Focus Group Two	Focus Group Three
Process Understanding (10)	Facility Design (6)	Unit Operations/Equipment (5)
Equipment Effectiveness/Six Sigma (8)	Project Management (5)	Project Management/CPMP (5)
Process Reliability (5)	Good Engineering Practices (3)	Technology Transfer (5)
Project Management (4)	Process Reliability (2)	Quality by Design/Facilities (4)
Automation (1)	Clean Rooms/Containment (1)	Process Control (4)

Table H. Priority subjects for Engineering Knowledge Domain.

Focus Group One	Focus Group Two	Focus Group Three
Financial Knowledge (9)	Financial Management (5)	Financial Knowledge (10)
Change Management (6)	Engineering Economics (5)	Business Ethics and Governance (6)
Risk Analysis (6)	Communication/Leadership (5)	Project Management Skills (6)
Decision Making/Prioritization (3)	International Relations/Culture (4)	Industry Overview (2)
Leadership and Relationships (2)	Risk Management (3)	Negotiation and Influence (2)

Table I. Priority Subjects for Business Management Knowledge Domain.

ments within a variety of courses rather than having dedicated course designs.

Subjects/Items in Knowledge Domains

Seven knowledge domains were analyzed by each focus group. After identifying all subjects that might underpin each of the focus groups, all participants voted for their priority preferences regarding the most important subjects in each domain. Tables C through I provide the results of the work of the focus groups as expressed in each group's rank order of rating for their top five subjects (votes shown in parenthesis). Many of the subjects prioritized by one group but not prioritized by the other groups were identified by those groups during their breakouts.

Compliance Knowledge Domain

In addition to the compliance subjects prioritized by the groups, the following other subjects were noted by two or more groups:

- Documentation
- Risk Assessment
- Safety, Health, and Environmental Regulatory

Development Knowledge Domain

In addition to the subjects prioritized, the following other subjects involving development were noted by two or more focus groups:

- Process Mapping and Automation
- Validation and Compliance

Manufacturing Knowledge Domain

Other manufacturing subjects mentioned by more than one focus group:

- SOPs and Training
- Supply Chain
- Data Management and Control

Supply Chain Knowledge Domain

Additional subjects concerning supply chain mentioned by more than one focus group:

- Specialty Distribution and Technologies (cold chain etc.)
- Security and Customs Requirements

Biological, Chemical, Manufacturing Science Knowledge Domain

No other science related subjects were identified by more than one focus group; however, some of the other subjects mentioned by singular focus groups were: Chemistry, Protein Chemistry, Statistics, and Intellectual Property.

Engineering Knowledge Domain

Three subject areas were identified by more than one focus group regarding engineering:

Focus Group One	Focus Group Two	Focus Group Three
Able to Maintain Focus	Aware of Limitations	Ability to Probe
Able to see Big Picture/Context	Challenge Convention/Status Quo	Ability to Manage Complexity
Accountable	Coaches/Teaches	Ability to Focus
Acts as Guide	Communicates (Even Tough Stuff)	Can do Attitude
Acts as Utility Player	Crosses Boundaries (no Silos)	Charisma
Asks the Right Questions	Delegates	Consensus Builder
Brings Others Along	Innovative	Creativity
Builds Relationships	Is Flexible	Curiosity
Delivers Results	Learner	Decisive
Effective Communicator (Listens)	Listener	Dedicated
Flexible	Manages Expectations	Genuine Interest in People
Harvests People's Energy	Non-confrontational	Good to Work With
Passionate	Open to New Ideas	Good Organizational Skills
Smiles	Positive and Motivated	Integrity
Tenacity and Perseverance	Responsiveness	Leader
Searches for Understanding	Listener	
	Self Starter	Keen Strategic Thinker
	Sense of Ownership	Respectful
	Sense of Urgency	Sense of Urgency
	Willingness to Make Decisions	Stability
	Trusting/Trustworthy	
	Understands Not Knowing it All	
	YES is favorite word	

Table J. Attributes associated with best-in-class co-workers.

- Soft skills including Writing and Presenting
- Site and Risk Management
- Standards and Regulations

Business Management Knowledge Domain

Areas of convergence that were not priorities in the business management domain were:

- Employee Relations
- Customer Service
- Metrics to Measure Performance

Observation of the priority areas shows that there is crossover of subjects across the knowledge domains. This indicates a variation in perspective about which domain the subject supports. It also implies an even higher priority for such areas as Project Management skills, Lean and Six Sigma, and Communication.

Attributes

The final element of the focus group process was the identification of attributes evident in those people currently working in industry who are seen as leaders and consistently utilize strong interpersonal and technical

skills. The results of these brainstorming sessions are shown in Table J.

Acknowledgements

ISPE, University of the Sciences in Philadelphia, and the authors want to once again thank all the members of the focus groups and their companies for participating in this process.

About the Authors



Jon Tomson, AICP is ISPE's University Relations Advisor. His primary responsibilities in this role include developing linkages between industry and academia, developing tools and information to support better communication between industry and academia, promoting industry involvement with academic initiatives, and fostering the ISPE's vision of the pharmaceutical Manufacturing Professional of the Future. Tomson was Chairman of the ISPE Board of Directors in 2001. He is an independent consultant specializing in facilitation, strategic planning, and strategic marketing. He can be reached via e-mail at jon@

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Matthew Wells is the Senior Director of Operations for AstraZeneca Pharmaceuticals in Wilmington, Delaware. He holds a BS in commerce and engineering sciences from

Drexel University and a MS in organizational dynamics from the University of Pennsylvania. As Senior Director of Operations, he is a member of the Operations Leadership Team and the Business Integrity and Assurance governance team. He is responsible for developing and monitoring short-term and long-term planning and continuous assurance processes. Prior to AstraZeneca, he worked for Johnson & Johnson in various supply chain management roles. He can be reached at matt.wells@astrazeneca.com.

AstraZeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE 19850. 

For more information on ISPE's Professional Certification Commission and the Certified Pharmaceutical Industry Professional™ (CPIP™) credential, please visit www.ispe-pcc.org.

SAFC to Expand cGMP Protein Purification Capacity

SAFC, a member of the Sigma-Aldrich Group, has announced that its SAFC Pharma business segment is expanding its cGMP protein purification capacity to meet increased market demand for therapeutic proteins from plant- and animal-sourced starting materials. Upon completion in April 2007, the natural and recombinant plant protein purification facility in St. Louis, Missouri, will be one of the world's largest therapeutic protein production sites.

SAFC, 3050 Spruce St., St. Louis, MO 63103, www.safcglobal.com.

Ronald Jones Joins Skanska

Skanska USA Building Inc. has announced that Ronald Jones joined the company as Senior Vice President, Commercial Director of the Life Sciences group, based in Parsippany, New Jersey. With a focus on design-build, Jones is responsible for overall account management, strategic planning, and developing new business in the pharmaceutical and biopharmaceutical markets – from construction to facility validation. A former Vice President of Lockwood Greene's global pharmaceutical and biotech business, Jones is a long standing member of ISPE, and is active on both national and local levels.

Skanska USA Building Inc., 1633 Littleton Rd., Parsippany, NJ 07054, www.skanskausa.com.

New Pharmaceutical Technology Consulting Firm Formed



Russ Somma

SommaTech LLC., an affiliate of IPS, is a new pharmaceutical technology consulting firm that helps clients achieve their FDA regulated product goals for a fast submission and seamless approval, as well as assuring a cost effective product and secure supply chain. Lead by Russ Somma, PhD, chair of the ISPE Professional Certification

Commission, SommaTech's team of specialists serve the pharmaceutical, biotechnology, medical devices, combination products, diagnostics, food supplements, and natural products industries. Key service areas are drug development, operations, and compliance.

SommaTech, 3 Executive Dr., 2nd floor, Somerset, NJ 08873, www.sommatechconsulting.com.

First GMP Facility for Biopharmaceutical Production in Malaysia Inaugurated



Visit of the modular facility by the Prime Minister and the Minister for Science, Technology and Innovation of Malaysia during the inauguration

At an inauguration ceremony on 7 September, Pharmaplan celebrated the first GMP facility for biopharmaceutical production in Malaysia. With this modular plant, Pharmaplan's customer Inno Biologics in Putra Nilai, Malaysia is at the forefront of the biotechnology effort in Malaysia. Inno Biologics, a subsidiary of Inno Bio Ventures, incorporated by the Ministry of Finance of Malaysia, is a manufacturing organization covering all stages of production of mammalian cell-based therapeutic proteins and monoclonal antibodies.

Pharmaplan GmbH, Borckenberg 14, 61440, Oberursel, Germany, www.pharmaplan.com.

GE Fanuc Teams with SAP

GE Fanuc Automation has announced the completion of a sales and marketing agreement with SAP America, Inc., to jointly market GE Fanuc Production Management solutions and SAP applications easing plant floor and enterprise integration to increase quality, drive productivity, and enable success in key business initiatives such as Lean Six Sigma, regulatory compliance, and

efficiency. This new relationship allows both companies to leverage each other's strengths to meet the needs of customers with the development of specialized professional services in order to support customers with planning, design, and implementation of the solutions.

GE Fanuc Automation, Inc., 2500 Austin Dr., Charlottesville, VA 22911, www.gefanuc.com.

SAP America Inc., 3999 W. Chester Pike, Newtown Sq., PA 19073, www.sap.com.

Pall to Expand Life Sciences Manufacturing in Puerto Rico



Eric Krasnoff, Chairman and CEO of Pall Corporation and the Hon. Anibal Acevedo-Vila, Governor of the Commonwealth of Puerto Rico.

Pall Corp., a global leader in filtration, separations, and purification, announces plans to expand its Life Sciences manufacturing operations in Fajardo, Puerto Rico. The planned establishment of a Life Sciences Center of Excellence will significantly expand Pall's capacity on the island, enhancing its ability to meet the increasing demand for its high quality technologies by the world's leading pharmaceutical and biotechnology companies, blood centers, and hospitals. Pall expects to invest around \$50 million in facilities, machinery, and equipment and add more than 250 full-time jobs in Puerto Rico by the year 2010.

Pall Corp., 2200 Northern Blvd., East Hills, NY 11548, www.pall.com.

Millipore Opens \$50 Million Research and Development Center



Millipore Corp., a leading provider of products and services that improve productivity in the laboratory and in biopharmaceutical manufacturing, has announced the opening of a new \$50 million research and development center in Bedford, Massachusetts. The research center will support the needs of Millipore's global customers who are involved in life science research and the production of biopharmaceutical drugs. With the opening of the new center, Millipore is able to develop full-scale

applications performance data and processes that simulate commercial conditions, ultimately resulting in increased speed and quality of biopharmaceutical production for their customers.

Millipore Corp., 290 Concord Rd., Billerica, MA 01821, www.millipore.com.

RFID TagSource and Confidex Announce Representation Agreement

RFID TagSource, a full-service provider of RFID tags and consulting services and Confidex, a fast-growing company with expertise in RFID design, manufacturing, and engineering, have announced an agreement designating RFID TagSource as Confidex's representative in North America. Under the terms of the agreement, RFID TagSource will provide Confidex's North American customers with a wide range of tagging services designed to support their unique RFID application requirements.


RFID TagSource, Waterfront Technology Center, 200 Federal St., Suite 300, Camden, NJ 08103, www.rfidtagsource.com.

Confidex Ltd., Pirkkalaistie 1, 37100 Nokia, Finland, www.confidex.fi.

SP Industries Announces Acquisition of FTS Systems

SP Industries has announced that it has acquired FTS Systems in Stone Ridge, New York. FTS Systems is a leading manufacturer of precision thermal control systems serving the pharmaceutical, biotechnology, educational, industrial, semiconductor, and OEM markets. The acquisition significantly increases SP's leadership position in freeze drying products and technology. The value of the acquisition was not disclosed.

SP Industries, 935 Mearns Rd., Warminster, PA 18974, www.spindustries.com.

FTS Systems, 3538 Main St., Stone Ridge, NY 12484, www.ftssystem.com. 

Control Valve



Spirax Sarco has released a new general service control valve, the Spira-Trol™. With its fully modular design, the two-port Spira-Trol control valve is engineered for refined performance and wide rangeability in applications including food and beverage, pharmaceutical, rubber, plastics, metals, chemicals, and electronics manufacturing. Both ANSI and EN versions share the same internals, and only three pneumatic actuators are required for valves up to 4 in. (100 mm) in size.

Spirax Sarco Inc., 1150 Northpoint Blvd., Blythewood, SC 29016, www.spiraxsarco.com/us.

Hygienic Pump



Watson-Marlow Bredel, the leading manufacturer of peristaltic pumps, introduces its 800 Series pumps for sanitary, high-performance applications in the pharmaceutical industry. These pumps are ideal for a variety of applications, including fermentation, cell culture, filtration, and separation. Capable of pumping amounts up to 8,000

liters/hour with pressures to 51 psi, the high-flow 800 Series is both CIP and SIP capable, enabling in-line cleaning at full velocity.

Watson-Marlow Bredel Inc., 37 Upton Technology Park, Wilmington, MA 01887, www.watson-marlow.com.

Hygienic Turbidity Sensor



With the new InPro 8600 series, Mettler-Toledo Ingold introduces a new technology platform for the reliable measurement of turbidity in hygienic applications. The turbidity sensors are based on combined 25° (forward)/90° (sideward) scattered light technology, which enable measurements in liquids which seem to be clear to the human eye. Distinction between turbidity caused by colloidal and larger particles is made possible with the dual angle measurement.

Mettler-Toledo Ingold, 36 Middlesex Turnpike, Bedford, MA, 01730, www.thorntoninc.com.

Retorquer



NJM/CLI introduces the new beltorque™, a unique high-speed


retorquer that reapplies cap torque after induction sealing. Unlike conventional retorquers that use discs or spindles to tighten caps, the patent-pending beltorque uses belts to tighten caps. Ideal for pharmaceuticals, nutraceuticals, cosmetics, and personal care products, beltorque handles round, oval, square, and rectangular containers from 2 to 12 inches in height and from 0.5 to 7 inches in diameter with caps up to 5 inches in diameter at speeds up to 300 cpm.

NJM/CLI, 56 Etna Rd., Lebanon, NH 03766, www.njmcli.com.

Dissolved Ozone Sensor



The use of dissolved ozone in the production of pharmaceutical water is being used more widely due to its efficient microorganism destruction capability and decomposition of resulting endotoxins. In order to meet the need for using stainless steel components in pharmaceutical water systems, Mettler-Toledo Thornton announces a new dissolved ozone sensor with stainless steel housing.

Mettler-Toledo Thornton, 36 Middlesex Turnpike, Bedford, MA, 01730, www.thorntoninc.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.*

ISPE Elects Board of Directors for 2006-2007

ISPE has elected its 2006-2007 International Board of Directors, which is responsible for creating the Society's vision, establishing its basic goals and policies, approving its financial direction, and providing guidance to ISPE Councils, Committees, Task Teams, and Professional Staff.

The Board was elected in late September, but was officially named at the 2006 ISPE Annual Meeting in Orlando, Florida, USA.

Newly Elected Officers

Chair: Jane R. Brown is Manager, GMP Compliance for GlaxoSmithKline in Research Triangle Park, North Carolina, USA.

Vice Chair: Bruce Davis is Global Capital Director for AstraZeneca in the United Kingdom. His current responsibilities are for the company capital program, covering all global business areas including Operations, R&D, and Commercial.

Treasurer: Charles P. Hoiberg is the Executive Director for Global Regulatory Portfolio and Projects in Pfizer's Global Regulatory CMC and QA Group.

Secretary: Alan Mac Neice is Project Director for Biologics at Elan's Biopharmaceutical Science's campus in Ireland.

Newly Elected Directors

Joan Gore
Tomiyasu Hirachi
John Nichols

Returning Directors

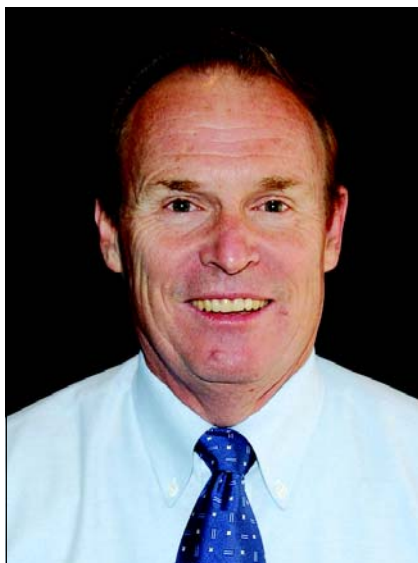
Gert Moelgaard (*immediate past chair*)
Bob Chew
Jan Gustafsson
Linda McBride
Randy Perez
Andre Walker
Stephanie Wilkins
Chris Wood



Chair: Jane R. Brown



Vice Chair: Bruce Davis



Treasurer: Charles P. Hoiberg



Secretary: Alan Mac Neice

Chairman

Jane R. Brown is Manager, GMP Compliance for GlaxoSmithKline in Research Triangle Park, North Carolina, USA. She has been involved in Quality Assurance/Regulatory Compliance in the pharmaceutical and medical device industries for more than 20 years.

Brown has been a member of ISPE since 1993, and has served on the Board of Directors for the Carolina-South Atlantic Chapter and as President of that Chapter. She has served on the International Board of Directors since

2000 and currently holds the position of Vice Chairman. She founded Student Chapters at North Carolina State University, the University of North Carolina, Duke, and Campbell Universities, and assisted in the formation of Chapters at Clemson, James Madison, and NC A&T Universities.

Brown was Co-Chair of the Student Affairs Task Team, and now is a member of the Student Development Committee and the University Relations Committee. She also is Board Liaison for the North American Affiliate Coun-

Continued on page 2.



ISPE Elects Board of Directors for 2006-2007

Continued from page 1.

cil. Brown is a member of the Industry Advisory Council for the Food Science Department at NC State University, where she earned a BS degree. She also is a member of the BioNetwork Industry Advisory Board for the North Carolina Community College System and a member of the Advisory Council for the Food Systems Leadership Institute.

"In 2005 we celebrated the first 25 years of ISPE. 2006 is the first year of our next 25 years, and we look forward to a future of continued growth and success. Our membership continues to expand worldwide and we are committed to developing professionals to bring innovation to the Life Sciences.

The future of our industry is changing and strategically we are well-positioned to influence this change in a positive manner. We have many exciting opportunities awaiting us to further develop our relationships with the FDA and other global regulatory agencies, as well as to build new relationships with academic institutions. These relationships will be critical in shaping the future of our industry.

We encourage global membership by supporting the development of new Affiliates and Chapters, and we plan for the future by recruiting student members and members of academia. As we look back at the past 25 years, we should be proud of our accomplishments and the influence we have had in shaping our industry. Now, we must look ahead into the future and continue to be a "Catalyst for Change."

We have developed a new Strategic Plan for the Society, and as Chairman, I will ensure that we implement the actions necessary to carry it forward. We also must continue to be attentive to the needs of our membership and prioritize our goals to meet them.

I will encourage the development of strategies and initiatives that continue to position ISPE to attract members from all aspects of our industry, to provide opportunities for students and academia, to build relationships with regulatory agencies, and to provide 100

percent customer satisfaction for our Members."

Vice Chairman

Bruce Davis works for AstraZeneca in the United Kingdom. His current responsibilities are for the company capital program, covering all global business areas including Operations, R&D, and Commercial. He also manages various internal business projects and has an external role including his commitment to ISPE.

Davis is a professional engineer, and prior to the above responsibilities, he worked in a range of other businesses, mainly in the engineering field, where he was responsible for new formulation assets internationally. He has wide international knowledge and has been involved in sterile, oral solid dosage, packaging, and bulk plants and laboratories in many countries in the continents of America, Europe, Asia, and Australasia.

He has chaired the ISPE Technical Documents Committee and is now a member of the Technical Documents Executive Committee. He chaired the Task Team that wrote the ISPE Baseline® Guide on Sterile Manufacturing Facilities, and also is chairing the team that is currently updating this Guide. He has given many presentations and organized educational events for ISPE in the US, Europe, and Australia. He has completed five years as a member of the ISPE International Board of Directors. Regarding other organizations, he also is secretary to the ASTM E55.03 Committee.

"The healthcare industry continues to change rapidly in terms of product complexities, regulatory and government demands, and cost pressures. The impact of this is wide-ranging - there is increased pressure to continue to develop more complex drugs, to launch them more quickly, and to develop effective supply chain. The use of PAT methods and other technologies to support the Quality by Design initiative is a growing area.

This has meant professionals within

the industry need to be highly adept at managing business, technological, and international demands. ISPE has a significant role to play in supporting and helping such professionals. Our volunteer status, our international presence, and our links with the regulators enable ISPE to take a lead in providing the training and education that our industry wants - be it international events, local seminars, or publications.

Many of our speakers are recognized experts within their field and their involvement plays a significant role in informing, developing, and guiding people. As Vice Chairman of ISPE, I would support the leadership of the Chairman and encourage the Society to continue to manage its affairs in as professional way as possible.

I also would continue to encourage greater understanding and communication internationally to ensure ISPE can help the people involved in our industry - be they from large companies or small ones - to be trained to achieve the highest professional and technical standards, at the same time maintaining excellent relationships with the Regulators."

Treasurer

Charles P. Hoiberg is the Executive Director for Global Regulatory Portfolio and Projects in Pfizer's Global Regulatory CMC and QA Group. He received a Bachelor of Science in chemistry from the College of William and Mary and a PhD in biochemistry (chemistry minor) from the Pennsylvania State University. He worked for more than eight years at Sterling Drug Inc. in research and development before joining the US Food and Drug Administration.

Hoiberg had a leadership role and held numerous positions in the Agency and was involved in numerous global initiatives. When he retired from the Agency, he was the Deputy Director of the Office of New Drug Chemistry and the Associate Director for International Activities. He was the CDER ICH Quality Coordinator. He represented the

Continued on page 5.

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ISPE/PDA Conferences to Examine Guidances for Pharmaceutical Industry with ICH Experts

ISPE has partnered with the Parenteral Drug Association (PDA) to co-host the first in a series of scientific conferences addressing the International Conference on Harmonisation's (ICH) Q8 and Q9 Pharmaceutical Development and Quality Risk Management Guidance.

Challenges of Implementing Q8 and Q9 – Practical Applications, will be held 6 to 7 December 2006 in Washington, D.C., USA. The conference will be presented again 12 to 13 February 2007 in Brussels, Belgium.

Members of the ICH Expert Working Groups who wrote "Q8 Pharmaceutical Development" and "Q9 Quality Risk Management" have been enlisted to develop content and give presentations for the upcoming joint ISPE/PDA Conferences.

Regulators from the US Food and Drug Administration (FDA), the European Agency for the Evaluation of Medicinal Products (EMA), and Japan's Ministry of Health, Labor and Welfare (MHLW) will participate in the Conferences. Co-hosts ISPE and PDA have joined forces to further explore the recently published Guidances for Industry, ICH Q8 and Q9.

The FDA issued Q8 on 22 May 2006, and just two weeks later, issued Q9. The Guidances for Industry are expected to have a major impact on how the industry and those who regulate it will do business.

"I am pleased we are able to join forces with PDA to produce these important events," said Bob Best, President and CEO of ISPE. "By combining our expertise on these subjects we will be able to better serve the industry. I would also like to thank the members of the ICH negotiating team represented by regulators and industry for their participation in developing this program."

"We are excited about the opportunity to work with ISPE on this initiative," said Robert Myers, PDA President. "These Conferences will enable both organizations to leverage our strengths to provide high-level scientific forums that will be mutually beneficial to our members and the pharmaceutical and biopharmaceutical community."

Conference developers explain that the event is designed to take attendees on a "back-stage tour" of the ICH negotiating table, looking at not only what is in the Guidances for Industry, but also at what wasn't included and why. Nearly 15 representatives of the ICH Expert Working Groups are involved in the conference planning and presentations.

Regulators from the US, Europe, and Japan will discuss how to:

- conduct science and risk-based assessment of submissions
- balance expectations for a quality by design-based submission and approval of a product without raising the bar

- provide regulatory flexibility while still assuring product quality
- handle legacy products

Industry representatives from each region will provide their perspectives on the challenges associated with the implementation of the Guidances, including a review of the potential benefits, such as enhanced process capability and robustness, better integration of review and inspection systems, achieving greater flexibility in specification setting, and the management of post approval changes.

In addition, through case studies, attendees will learn from regulators and industry representatives about experiences with the FDA's CMC Pilot Program, and the implementations of strategies for quality risk management.


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Seminars to Focus on Facilities and Biotechnology

Mark your calendars for next year's Tampa Conference, which will be held 12 to 15 February 2007 at the Hyatt Regency Tampa Bay in Tampa, Florida, USA. The seminars will focus primarily on Facilities and Biotechnology. Choose the seminars that you want and need to enhance your professional development.

Seminars will include:

- Risk Assessment as a Tool of Design, Implementation, and Management of Critical Utilities
- Renovation of Pharmaceutical Facilities – API, Biotechnology, and Pilot Plant
- The Latest in Processing Technologies for Sterile Drugs
- Design and Operation of Biotech Upstream-Downstream
- GAMP Electronic Records: An Update on Part 11 with a Focus on Risk Management
- Advances in Oral Solid Dosage Manufacturing
- Current Trends and Issues in Validation
- Baseline® Guide: PACLAW Review of Guide from Developers (New for 2007)
- Sterile Manufacturing Facilities: Latest Innovations and Industry Development

For complete seminar listings and to register, visit www.ispe.org, or call ISPE customer service at tel: +1-813-960-2105. 

ISPE to hold Brussels Conference, 4-7 December 2006, Brussels, Belgium

The ISPE Brussels Conference will be held at the Sheraton Hotel 4 to 7 December 2006, bringing together the pharmaceutical industry from around the world to focus on key topics from the industry.

This ISPE event will offer an outstanding program with sessions presented by an international roster of key industry leaders.

The GAMP® seminar will examine effective compliance through understanding and management of customer/supplier relationships, including the benefits and risks of leveraging supplier effort and documentation.

The Sterile Product Processing Seminar will provide background information, new technology updates, case studies, and the opportunity for discussion on key issues influencing operations in the field of advanced aseptic processing.

The Containment Technology Seminar will explore the latest developments used in the containment of potent compounds for the manufacture of bulk active pharmaceutical ingredients and the production of drugs in their final dosage form together with R&D facilities. Leading international speakers will provide a global perspective of recent developments in the regulatory expectations for compliance.

The optimization of oral solid dosage processes and technologies also will be discussed at the Conference,


including current technology being developed for use in oral solid dosage form process technology. Product development and processes employed in the manufacture of an oral solid dosage form will be addressed with particular focus on continuous processing, Process Analytical Technology (PAT), and containment approaches.

Furthermore, in the Baseline® Pharmaceutical Engineering Series two guides will be discussed. The *Bulk Pharmaceutical Chemicals Baseline Guide*, originally published in June 1996, has undergone a complete revision. This seminar will present some of the key changes and will allow delegates an opportunity to interact with the authors in a workshop scenario.

The new *Packaging, Labelling, and Warehousing Operations Baseline Guide* will be introduced by the members of the Task Team. They will present the chapters of the Guide, including the influence of architecture, HVAC, process support, utilities, and equipment qualification on the design of new and renovated facilities. During this seminar, a representative of MHRA also will present the latest regulatory challenges facing manufacturers.

The Conference also will include several networking opportunities and a table top exhibition, representing more than 40 companies.


For full program information and to register, please visit www.ispe.org/BrusselsConference or contact:

ISPE Registration Services
Avenue de Tervueren, 300, B-1150 Brussels, Belgium
Tel : +32 2 743 4422 , Fax : +32 2 743 1550
E-mail: europeregistrations@ispe.org 

How do you like our driving?



You were one of 37,000 worldwide who read the inaugural issue of the *Journal of Pharmaceutical Innovation*, our international scientific peer-reviewed publication focusing on new and innovative technologies in pharmaceutical manufacturing. But you may have missed the section where we asked for your feedback.

Please fill out the survey, located in your copy of *JPI* or complete it on-line at www.ispe.org/jpi. It takes two minutes and it will help us steer YOUR publication in the right direction. 

ISPE to Co-host FDA Pharmaceutical Quality Initiatives Program with AAPS

ISPE will co-host the US FDA's "Pharmaceutical Quality Initiatives – Implementation of a Modern Risk-Based Approach" on 28 February to 2 March 2007 at the Bethesda North Marriott in North Bethesda, Maryland. The event will be co-sponsored with AAPS.

This workshop is a follow-up to the PQRI/FDA Workshop on "A Drug Quality System for the 21st Century" held April 2003. It is being planned under the auspices of the Council on Pharmaceutical Quality at the US FDA.

The two-and-a-half-day program is intended to present progress on the FDA's pharmaceutical quality initiatives. Furthermore, the workshop will allow regulated industry, other stakeholders, and the public to comment on progress made and to provide input to facilitate implementation of a common vision for pharmaceutical manufacturing in the 21st century. Among topics to be addressed: pharmaceutical de-

velopment, Chemistry, Manufacturing, and Controls (CMC), manufacturing and quality operations, Good Manufacturing Practices (GMPs), quality systems, and quality assurance.

This workshop will:

- discuss US FDA's quality initiatives and share progress made since the issuance of the Agency's 2004 report, "Pharmaceutical cGMPs for the 21st Century – A Risk-based Approach,"
- provide updates from the US FDA's Council on Pharmaceutical Quality, with a focus on implementation challenges and remaining issues, and
- seek input and recommendations from stakeholders

Check www.ISPE.org for updates. 

ISPE Elects Board of Directors for 2006-2007

Continued from page 2.

Agency in negotiations of many ICH topics and has had close contacts with many worldwide regulators and industry leaders. While at the Agency, he was very involved in working with ISPE on developing the SUPAC Equipment Addendum.

Hoiberg has been a frequent lecturer for ISPE at its domestic and international programs in Europe and Asia, and is currently the Secretary for the ISPE International Board of Directors.

"For future membership growth and increased importance, ISPE faces several daunting challenges given the changing environment of the pharmaceutical industry and the regulatory agencies. Pressures are increasing on the global industry to develop new drugs, reduce manufacturing costs, and incorporate innovative approaches, such as process analytical technology, quality by design, and design space. Likewise, the regulatory agencies are reassessing their approval processes and GMP practices and reengineering for the 21st century.

Given ISPE's highly technical membership, its excellent conferences and training programs, and its good relations with the regulatory authorities, ISPE has a great opportunity to play an integral role to ensure success for itself

and the pharmaceutical community. As Treasurer of ISPE, I will professionally manage the Society's finances."

Secretary


Alan Mac Neice is Project Director for Biologics at Elan's Biopharmaceutical Science's campus in Ireland. Previously, he was Director of Engineering for the campus for more than seven years. During his career, Mac Neice has held responsibilities for capital projects, maintenance, facilities, safety and environment.

Mac Neice holds a degree in chemical engineering and a number of business qualifications including an MBA. His 22-year career has been within the manufacturing sector of the pharmaceutical industry. He has worked with five different US and European multinationals, in a diverse range of manufacturing operations including chemical APIs, biotechnology APIs, aseptic dose forms, oral solid dose forms, and the extraction of natural medicines.

A member of the Ireland Affiliate since 1992, Mac Neice has been a committed participant at ISPE activities as an organizer, speaker, and advisor. From 1998 to 2004, Mac Neice served on the Irish Affiliate Management Com-

mittee, including a two-year term as Chairman. Under his stewardship, the Affiliate membership grew by 60 percent and the first Student Chapter outside of North America was established.

"I believe the most significant challenge facing the pharmaceutical industry is to free itself of the inertia that is associated with change throughout the industry. The environment is ready for this to take place with the promotion of initiatives such as PAT and risk-based approaches. ISPE is one of few organizations that can bring significant change to the culture of the industry. The industry needs a champion for innovation and initiative. ISPE has had an enormous impact on the competence of industry professionals and the standardization of industry practice around many issues.

It is time to meet the challenge of creating a more dynamic industry by steering our industry organizations and its professionals to a new mindset of greater innovation and initiative. As Secretary of ISPE, I will have a vision of new challenges and how they might be met. I also understand the stewardship required to sustain the organization that ISPE has become." 

Science-Based Manufacturing for the Next Decade

A Review of the Plenary Day of the ISPE Vienna Congress

by Mike Bennoson

During the Plenary Day of the ISPE Vienna Congress held 18 to 22 September, senior executives from the global pharmaceutical industry, US and European regulators, and Academia provided major insights into the challenges facing the industry with science-based manufacturing over the next decade.

In the morning session, the importance and opportunities for science-based manufacturing were addressed, a European (EMEA) regulatory perspective was given and global trends detailed. In the afternoon, an academic viewpoint was provided, an FDA presentation on PAT, and a comprehensive review and update on ICH initiatives were detailed. The Plenary Day concluded with a presentation on the pharmaceutical manufacturing professional of the future, the vision of which is that future professionals supporting manufacturing will require new applied scientific process and engineering skills.

The co-leaders for this Plenary Day were ISPE Chair Gert Moelgaard and ISPE Secretary Charles Hoiberg.



Meeting the Challenges of the Next Decade – Key Role for Science Based Manufacturing

Professor Trevor Jones indicated that while the pharmaceutical and biotechnology industries continue to be suc-

cessful, the climate in which they now operate demands a continuous evaluation of both the efficiency and effectiveness of manufacturing processes and technologies.

The external pressures of changing market demands that companies reconsider how best they can ensure a competent science base in manufacturing. Although new formulations are science-based in their construction and composition, their performance in routine production can only be evaluated after sufficient experience in large scale manufacture. In addition, for many research-based companies, the product mix of conventional and specialized dosage forms is likely to change as more products of biotechnological origin enter the market. This will result in an increased demand for dedicated technology, higher requirements for science-based process and engineering, and an increase in sterile products technology.

In conclusion, the need for science-based manufacture has never been more important.

Science-Based Manufacturing – The EMEA Regulatory Perspective

The roles and responsibilities of the European Medicines Agency (EMA) within the European and global regulatory environment were described by Francois Xavier Lery.

EMA was established in 1995 and represents a unique concept of networking more than 40 EU National Competent Authorities (NCAs) in Europe with activities in scientific assessment, monitoring of authorized medicines, and harmonization of technical requirements.

An EMA road map to 2010 has been issued to strengthen the EMA



networking model and to address the new challenges for the EU regulatory system, EU enlargement, and new technologies.

Implementation of new legislation in GMP and regulatory texts that have been recently put into force were detailed. ICH Q8, Q9, and Q10 were described and it was indicated that these guidelines represent an opportunity to use new concepts and paradigms such as Design Space, Quality by Design, Control Strategy, and Quality Risk Management. The European PAT team was described which was established as a forum for dialogue and understanding between quality assessors and inspectors in this emerging field.

In conclusion, Europe has a long tradition of international work which should be strengthened through development of global ICH guidelines, cooperation, exchange, and training in coordination with other authorities and networks such as WHO, US FDA, PIC/S, etc. The main focus in respect of science-based manufacturing will be the implementation of global ICH guidelines and submission of Quality by Design and PAT submissions.

Global Perspectives for the Pharmaceutical Industry

Allister Clark gave an overview of both the performance and key themes across the global pharmaceutical industry. The presentation focused at the level of the

Science-Based Manufacturing...

Continued.

market and assessed performance of pharmaceutical product sales worldwide. A synopsis of the R&D pipeline was detailed and compared against historical performance. Key cost containment forces, pricing policies, and the performance of generic market were described.

Overall market trends, by geography, identifying regions of especially high growth were detailed and also the evolution of regional and therapy area performance by 2009 – market growth is being driven by specialist products, oncology medicines, as well as products of biotechnology origin. Future generic availability will occur given upcoming patent expiries. The topic of biogenerics, an emerging theme of today and one set to gather momentum was discussed.

In conclusion, understanding future trends is critical for companies to build appropriate organizational designs for the future.

Opportunities and Challenges Associated with an Improved Science Base for API Manufacture

Professor Kevin Roberts reviewed the industrial relevance related to crystal science and engineering associated with pharmaceutical manufacturing highlighting the opportunities afforded by ICH Q8 and Design Space. The need for an integrated manufacturing strategy was stressed by utilizing the 4 Ms concept (Model, Measure, Manipulate, and Manufacture). Experimental studies using PAT techniques in manufacturing to improve utility and quality of crystallized material were described.

The importance and value of industry and academic links both in training and research were highlighted in order to develop new science-based approaches to drug manufacture.

PAT – A Model for Science Based Manufacturing

Chris Watts gave the background and history of PAT, the regulatory expectations, the impact of PAT for pharmaceutical manufacturing, and the fu-



ture challenges and opportunities for PAT.

The FDA rationale for PAT was described, which included an increasing burden on FDA resources with more than 4,000 manufacturing supplements annually, the inability to meet statutory biennial GMP inspection requirements, and the lower scrutiny on United States industry. In addition, the public health aspects of product recalls were a factor.

The focus of PAT is the understanding and controlling the manufacturing process.

A Review and Update on ICH Initiatives

John Berridge gave a comprehensive and provocative review of the ICH guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality Systems). These support a vision of an integrated pharmaceutical quality system that results in a significant decrease in the intensity of regulatory oversight.

Q8 marks a paradigm shift in quality guidelines as it is much less directive and describes a desired state where manufacturers have an enhanced understanding of products and processes. Adoption of the principles in Q8 can lead to an enhanced regulatory flexibility compared to the current situation.

Q9, while not describing anything significantly new, formalizes many of the approaches used by industry for risk management. Q9 supports Q8 and other guidelines and provides encour-

agement for companies to share their risk management approaches with the authorities.

Q10 is at an early stage of development and is intended to describe the expectations of a modern, robust pharmaceutical quality system.


In conclusion, it is clear that the combination of Q8, Q9, and Q10 yields an opportunity within the industry, which is to facilitate empowerment of the industry to manage a much greater proportion of post approval changes and to support continual improvement without the constant inhibitions of needing to seek multiple regulatory approvals prior to implementation.

“...People will be manufacturing’s most valuable asset – they need to be developed in their formative years, attracted to our industry, nurtured, and allowed to flourish.”

Pharmaceutical Manufacturing Professional of the Future

Shawn Whitfield described the tremendous changes in the pharmaceutical industry which have brought new challenges and raised expectations. The prime focus of these changes has been an emphasis on science and risk-based approaches. As a result, the manufacturing professional of the future will be very different from the traditional model of today – key business, economic and emerging and developing technologies, as well as the PAT led Quality by Design expectations are generating the need to raise the capability of the manufacturing professional.

The skills, competence, and experience needed by such individuals are already in high demand, but in short supply with much competition for talented scientists and engineers.

In conclusion, people will be manufacturing’s most valuable asset – they need to be developed in their formative years, attracted to our industry, nurtured, and allowed to flourish. 



Submissions for Facility of the Year Awards (FOYA) Due 8 December

ISPE, along with INTERPHEX and *Pharmaceutical Processing* magazine, is seeking submissions for its global 2007 Facility of the Year Awards (FOYA) competition.

Pharmaceutical manufacturing organizations should submit plans of newly constructed or renovated facilities that showcase cutting-edge engineering, innovative new technology, or advanced applications of existing technology.

FOYA, in its third year, is an annual competition to recognize state-of-the-art pharmaceutical manufacturing projects that utilize new and innovative technologies to enhance the delivery of a quality project, as well as to reduce the cost of producing high-quality medicines.



FOYA was instituted to recognize accomplishments, and share commitment and dedication of individuals in companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of all global consumers.

“We want to give recognition to those who design, build, and operate world-class pharmaceutical manufacturing facilities,” said Scott Ludlum, ISPE’s Director of Business Initiatives. “And this year, the Awards have expanded in order to raise awareness for these vital segments of the global pharmaceutical industry.”


This year, several significant enhancements have been added to the Awards program, including six awards categories in:

- Process Innovation
- Project Execution
- Equipment/Innovation
- Facility/Integration
- Energy Management
- Operational Excellence



In addition to the new categories, winners will be recognized and introduced during INTERPHEX 2007, 24 to 26 April in New York City, where thousands of attendees convene for one of the largest industry events worldwide.

The deadline to submit applications for the 2007 competition is 8 December 2006. For complete information about the Awards program and submission procedures, as well as to download the on-line application form, please visit www.facilityoftheyear.org. Specific questions can be addressed to Scott Ludlum, ISPE Director of Business Initiatives, by tel: +1-813-739-2284 or by e-mail: sludlum@ispe.org.

The announcement of the overall winner of the coveted Facility of the Year Awards competition will take place at ISPE’s Annual Meeting in November 2007 at Caesar’s Palace in Las Vegas. A Facility of the Year Awards display will feature the Category Winners and Facility of the Year Awards winner. The winner will receive the prestigious crystal and marble trophy, as well as various publicity initiatives through ISPE, *Pharmaceutical Engineering*, INTERPHEX, and *Pharmaceutical Processing*. Key contributing organization also will be included in overall publicity. 

Communities of Practice Bring Professionals Together

Have you signed up for your Community of Practice yet? If not, you may be missing out. ISPE recently launched Communities of Practice to allow members to target their needs by joining like-minded professionals to exchange ideas about their fields.



ISPE understands the critical need of professionals to know the industry, particularly when it comes to tracking emerging trends. By joining an ISPE Community of Practice (COP), members have instant access to a network of like-minded practitioners who want to learn and work together to address regional, domestic, and global issues in their particular areas of expertise.

ISPE COPs offer pharmaceutical manufacturing professionals a dynamic forum to gain relevant and timely information through discussions and networking opportunities. The purpose of ISPE COPs is:

- Provide a forum for community members to help each other solve everyday work problems and engage in active networking.
- Develop and disseminate best practices, guidelines, and procedures for use by community members
- Organize, manage, and research a body of knowledge from which Community members can draw
- Innovate and create breakthrough ideas, knowledge, and practices

To find out more about Communities of Practice, or to join one or more, please visit www.ispe.org. 

ISPE and Genentech Program Use Chocolate and Enzymes to Build Kids' Interest in Science

Last May, representatives from ISPE and Genentech – loaded with Styrofoam, pipe cleaners, Popsicle sticks, and chocolate – visited two South San Francisco schools, on a mission to bring practical science and engineering concepts and knowledge to classrooms and get kids interested in studying science and engineering as careers.

This new program is a collaborative effort among ISPE, Genentech, and the South San Francisco Unified School District, and is one of many ISPE initiatives to educate the pharmaceutical manufacturing professionals of the future.

The program, spearheaded by ISPE Member Melody Spradlin, can be replicated through lesson plans and brought to other elementary schools as well.

At Sunshine Gardens Elementary School, Spradlin and 10 project managers from ISPE and Genentech's Non-Manufacturing Project Engineering and Project Services groups led an instructional session and mini-construction project with 70 fifth graders. The students were given 30 minutes to build a simplified version of a chocolate factory from supplies that included Styrofoam, foam board, popsicle sticks, colorful pipe cleaners, funnels, colored paper, corrugated paper, glue, tape, ruler, and quick-drying molding clay.

According to the project managers working with individual groups, the students came up with imaginative, detailed designs and asked intelligent questions during the building process.

"The light in the kids' eyes when they connected to a scientific engineering idea was inspiring," said Spradlin. "They were so proud when they were able to master the topics we were teaching them. The project managers were so energized by their response and enthusiasm. We'll definitely do this again next year."



As Spradlin and her staff assembled lesson plans and examples for the project managers to follow, they discussed with the students math and science concepts ranging from electrical circuits and fermentation to water flow. They also discussed construction concepts, such as tension, compression force, and geometry.

The groups presented their chocolate factories to their classmates and school and city officials. Local chocolate and candy companies donated chocolate samples and ingredients, including cacao beans, raw sugar, and vanilla, while Genentech provided supplies and materials to build the chocolate factories.

ISPE and Genentech representatives also visited El Camino High School, where Dr. Claire Komives of San Jose State University facilitated a lab on enzymes. Komives specifically designed the lesson and lab, showing how enzymes absorb light and the rate of absorption.

"This is a lab for those interested in biology and who can tolerate math," said Komives. Students first mixed their enzyme solution, then used a spectrophotometer to analyze absorption rates and finally, used that data to graph the rates. Komives provided lab supplies and the spectrophotometers and Genentech's Research Department also donated supplies.

For more information on these projects, or to learn how you can bring these projects to your local schools, contact Melody Spradlin at +1-650-225-1799.

Special thanks to Jackie Kiouss of Genentech for her contribution to this report.





Mark Your Calendar with these ISPE Events

December 2006

- 4 Greater Los Angeles Area Chapter, Commuter Conference, Technical Training Series: Compendial Water at Amgen, LA Area, California, USA
- 4 - 7 **ISPE Brussels Conference, Sheraton Brussels, Brussels, Belgium**
- 6 New Jersey Chapter, Holiday Event, Dinner and Dancing on the Bateux, New York, USA
- 6 Carolina-South Atlantic Chapter, BBQ and Bioreactors, "Comprehensive Look at Bioreactor Basics up to Large Scale Design and Validation Issues," NC Biotech Center, North Carolina, USA
- 6 - 7 **ISPE/PDA Conference, "Challenges of Implementing Q8 and Q9 – Practical Applications," Omni Shoreham Hotel, Washington, DC, USA**
- 7 Rocky Mountain Chapter, Annual Holiday Party, Millennium Harvest House Hotel, Boulder, Colorado, USA
- 12 Delaware Valley Chapter, Holiday Party, USA
- 13 **On-line Seminar: Top 5 Critical Issues for PAT Professionals**
- 14 Italy Affiliate, Christmas Night, Italy

January 2007

- 18 **On-line Seminar: Clinical Trials: A Primer**
- 18 New England Chapter, BioPharma 2007, Keynote Speaker: Jerry Arthur, President, Cook Pharmica, Crowne Plaza, Warwick, Rhode Island, USA
- 27 Carolina-South Atlantic Chapter, East Coast Student Leadership Forum, McKimmon Center, USA

February 2007

- 1 - 2 INTERPHEX Puerto Rico, Puerto Rico Convention Center, San Juan, Puerto Rico
- 12 - 13 **ISPE/PDA Conference, "Challenges of Implementing Q8 and Q9 – Practical Applications," Radisson SAS Royal Hotel, Brussels, Belgium**
- 12 - 15 **2007 Tampa Conference, Hyatt Regency, Tampa, Florida, USA**
- 8 Carolina-South Atlantic Chapter, Student Career Fair, NC Biotech Center, North Carolina, USA
- 8 Greater Los Angeles Area Chapter, Facility Tour at Teva, Irvine, California, USA
- 22 Rocky Mountain Chapter, 12th Annual Vendor Exhibition and Workshop, Millennium Harvest House Hotel, Boulder, Colorado, USA
- 26 - Mar 1 **2007 Copenhagen Classroom Training, Radisson SAS Scandinavia Hotel, Copenhagen, Denmark**
- 28 - Mar 2 **ISPE/AAPS/FDA, Pharmaceutical Quality Initiatives - Implementation of a Modern Risk-Based Approach, Bethesda North Marriott Hotel and Conference Center, Bethesda, Maryland, USA**


Dates and Topics are subject to change 

ISPE/PDA Conferences...

Continued from page 3.

Representatives from both ISPE and PDA will provide updates on their respective associations' work relative to Q8 and Q9. Panel discussions will provide opportunities for interaction between speakers and attendees. The confer-

ences will be structured so that all attendees have the benefit of attending all sessions and hearing all presentations.

To register for the upcoming conference in Washington, D.C., visit www.ispe-pda.org/Q8Q9. 

Architects, Engineers - Constructors

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.

NNE US, 7868 Hwy. 70 W., Clayton, NC 27527. (919) 359-6600. See our ad in this issue.

Parsons, 150 Federal St., Boston, MA 02110. (617)-946-9400. 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 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

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.

Cal-Chem Corp., 2102 Merced Ave., South El Monte, CA 91733. (800) 444-6786. See our ad in this issue.

Passivation and Contract Cleaning Services (cont.)

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.

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 or Call 630.629.9900

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.

Valves/Fittings

ITT Pure-Flo, 33 Centerville Rd., Lancaster, PA 17603. (717) 509-2208. See our ad in this issue.

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Statement of Ownership, Management, and Circulation

1. Publication Title: **Pharmaceutical Engineering**

2. Publication Number: **0273-8139**

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8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not printer): **3109 W. Dr. Martin Luther King Jr. Blvd., Suite 250, Tampa, Hillsborough, Florida 33607**

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor (Do not leave blank):
 Publisher: **International Society for Pharmaceutical Engineering, Inc. 3109 W. Dr. Martin Luther King Jr. Blvd., Suite 250, Tampa, FL 33607**
 Editor: **Gloria Hall, Editor, Pharmaceutical Engineering 3109 W. Dr. Martin Luther King Jr. Blvd., Suite 250, Tampa, FL 33607**
 Managing Editor: **Gloria Hall (same as above)**

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12. Tax Status (For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)
 Has Not Changed During Preceding 12 Months
 Has Changed During Preceding 12 Months (Publisher must submit explanation of change with this statement)
 13 Form 9928, October 1999 (See Instructions on Reverse)

13. Publication Title: **Pharmaceutical Engineering**

14. Issue Date for Circulation Data Below: **July/August 2006**

Extent and Nature of Circulation		Average No. Copies Each Issue During Preceding 12 Months	Total No. Copies of Single Issue Published Nearest to Filing Date
A. Total Number of Copies (Net press run)			
(1) Total Number of Copies (Net press run)		24,719	25,000
(2) Paid and/or Requested Circulation (Sum of 5a(1) and 5a(2))		13,234	13,315
5a. Paid and/or Requested Circulation (Sum of 5a(1) and 5a(2))		0	0
5a(1) Outside-County as Stated on Form 3541		0	0
5a(2) In-County as Stated on Form 3541		0	0
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5b. Free Distribution (Sum of 5b(1) and 5b(2))		8,483	8,451
5b(1) Outside-County as Stated on Form 3541		0	0
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5b(3) Other Classes Mailed Through the USPS		0	0
5c. Free Distribution Outside the Mail (Sum of 5c(1) and 5c(2))		21,677	21,766
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5c(3) Other Classes Mailed Through the USPS		0	0
5d. Free Distribution Outside the Mail (Sum of 5d(1) and 5d(2))		2,942	3,234
5d(1) Outside-County as Stated on Form 3541		3,042	3,234
5d(2) In-County as Stated on Form 3541		0	0
5e. Total Distribution (Sum of 5a(2), 5b(3), 5c(3), and 5d(2))		24,719	25,000
5f. Copies not Distributed		0	0
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5h. Paid and/or Requested Circulation (Paid and/or Requested Circulation (Net press run) minus 5f)		87.7%	87.1%

15. Publication of Statement of Ownership: **EXPLANATION required: Will be printed in the Nov/Dec 2006 issue of the publication.** Publication not required

16. Signature and Title of Editor, Publisher, Business Manager, or Owner: **Gloria Hall, Editor** Date: **9-25-06**

17. I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

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