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The Challenges of Regulatory Change Management: Does ICH Quality Trio Provide the Solution?

by Mary Oates, Michael Marini, and Barry McCloy

It is hoped that this article will stimulate the necessary dialogue among industry and regulators to establish the baseline criteria to achieve a system in which the majority of changes can be made globally under the robust quality systems of a firm with total visibility to the health authorities upon request.

Introduction

Robust change management is a critical element of a strong pharmaceutical quality system. Accordingly, ICH Q10, "Pharmaceutical Quality System," describes it as a vital part of the lifecycle approach to product quality. However, in an environment of increasing globalization for both pharmaceutical firms and health authorities, regulatory change management presents significant challenges to all parties involved. This same globalization has resulted in ICH documents that may provide the solution to this complex issue. Individually, the ICH Quality trio of Q8, Q9, and Q10 provide significant benefits, including guidance on approaches to demonstrating process and product understanding throughout the product lifecycle, tools that can be used to assess and mitigate risk and a comprehensive description of a robust quality system. When applied collectively as part of a purposeful and cohesive approach, the benefits can be exponentially greater, including in the area of change management.

A regulatory change management system that is enabled by ICH Q8, Q9, and Q10 also will encourage and accelerate continuous improvement. Such a system would foster the identification of the critical few changes that must be approved by health authorities in advance of implementation and those that can be managed internally by the firm. Currently, many changes must be submitted to regulatory agencies for prior approval. This can discourage and undermine significant improvements, many of which simplify the manufacturing process and reduce uncertainty, from being rapidly implemented and result in nonconformance situations in some markets. Implementation of a regulatory change in multiple countries can be a conformance challenge given the differences in regulatory expectations governing the content of the change justification and the variety of review and approval times. If global approval is not received for a given change in a timely manner, a great deal of supply chain complexity can be introduced. Of even more importance, a firm could be placed in a position of nonconformance in those countries that have approved the change due to the fact that some regulatory authorities expect implementation within a defined period of time post-approval (e.g., within six months). Firms are faced with the following options:

1. Implement change(s) only after approval has been received from all affected markets.
2. Maintain two separate processes at the manufacturing site; one for markets where the authorization to implement the change(s) has been received and a different process for markets where authorization to implement the change(s) has not been received. This may only be possible if both processes can be utilized concurrently and the resulting products can be adequately segregated and controlled to ensure that only the product produced for a specific market (or markets) is distributed into those markets.
3. Build sufficient inventory with the material manufactured via the current process in order to supply the countries where the change has not yet been approved, and implement the change to accommodate those markets that have already approved the change(s). In order to implement this approach, an accurate forecast of inventory is required to assure constant supply to those markets

that have not yet approved the change.

4. Implement change(s) to accommodate those markets that have approved the change(s) and accept that the site cannot supply "changed" material to those countries where prior approval is required, potentially resulting in the unavailability of medicine needed by patients for an undetermined period of time.
5. Not to pursue the change. A site could find it practically impossible to comply with all markets simultaneously; therefore, the most prudent option may be to maintain the current process for all markets.

Of the options discussed above, option 1 represents the ideal situation as this assures full compliance with all existing registrations and the site only has to manage one process/product. However, depending on the complexity of the change and the differing review periods by various health authorities, a site may find the change has been approved expeditiously (e.g., within a three month period) in some markets, while others are on an entirely different time schedule (e.g., up to two years). In these cases the site may find itself out of compliance with its registration in the early-approving markets.

Over time, the impact of the options available and the challenge to simultaneously comply with all markets in a practical manner results in sites, and on a larger scale, industry failing to take advantage of innovations in production and testing technology. Therefore, it is important that solutions to these challenges be identified and implemented.

An ideal solution to these challenges is a more agile and consistent global regulatory change management system that would be of benefit to industry, regulators and patients. One way to accomplish this is to provide firms the ability to internally manage the vast majority of changes that currently require regulatory approval prior to implementation provided a firm can demonstrate appropriate control over these changes and their impacts. The application of robust change management within the framework of ICH Q8, Q9, and Q10, specifically a strong pharmaceutical quality system combined with appropriate process knowledge and understanding and mitigation of risks, should enhance the confidence of global health authorities that firms have the ability to appropriately assess and implement changes internally with minimal regulatory involvement. In other words, is it possible for the firm to move into a "low risk" category for change management?

The key elements that firms should include in their change management process in order to demonstrate a high level of control and understanding are depicted in Figure 1. These include:

- A strong overarching quality system of which change management is one aspect (Q10).
- Active knowledge management (Q10).
- Tools and culture that support science-based risk assessments followed by appropriate decision-making (Q8, Q9).
- Organizational Agility (inherent in the ICH Quality trio).
- Timely and accurate internal and external communication (Q10).
- Management oversight of the performance of the change management system (Q10).

This article will provide insight into these critical components of a robust change management system and propose a solution to the current challenge of global regulatory change.

The Importance of an Overarching Quality System

Robust change management cannot exist in the absence of a strong, overall quality system. As defined in ICH Q10, other elements of the quality system include process performance and product quality monitoring, corrective and preventive actions, and management review of process performance and product quality. It is actually the outputs from these systems as well as scientific and technological advances that serve as stimuli for change. This relationship is illustrated in Figure 1. As the body of knowledge about a process and product grows from development to commercial manufacturing, monitoring and trending will likely result in increased opportunities for improvement. A strong mechanism must be in place to capture these stimuli for change. There also must be a process for identification and mitigation of any risks associated with proposed changes. Following approval and implementation, the impact of the modification (e.g., to parameters, specifications, procedures, etc.) will be assessed as part of routine monitoring and trending, adding again to the overall body of knowledge. Equally essential to change management is organizational agility, ensuring that changes can be made quickly and efficiently, having appropriate systems in place to control change and effective communication of changes, both within the firm, and where necessary, to external bodies such as regulatory agencies and customers. Management review of the overall process is key to maintaining the system's robustness.

Active Knowledge Management

No change management system can be successful without

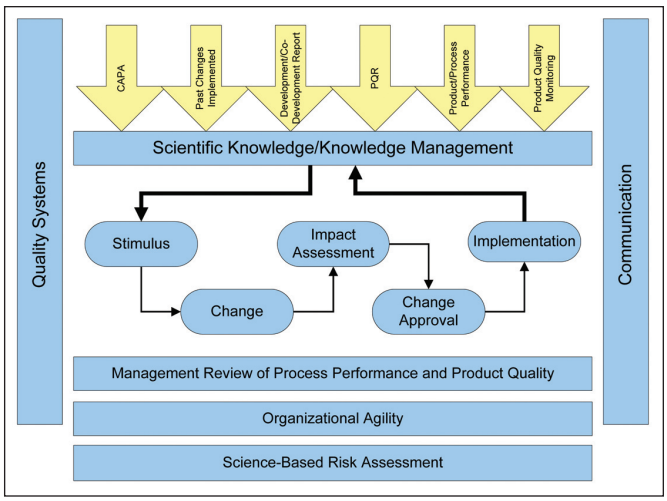

Figure 1. Elements and inputs of a robust change management system.

active knowledge management, described in ICH Q10 as an enabler of the quality system. Stimuli for change can be found in the inputs and outputs of many other systems and processes and must be captured, trended, understood, and used for continuous improvement. In addition to this proactive approach, the need for change also may be identified on an ad hoc basis as events occur. A well-designed change management system will allow for the identification and implementation of changes from both proactive and reactive sources. Management alone is not responsible for determining changes that may be needed; rather, every member of an organization must be vigilant in identifying opportunities for continuous improvement and sponsor their implementation via the change management process.

A listing of potential sources for change stimuli is given below. This listing is not intended to be comprehensive and it should be recognized that other opportunities exist to identify opportunities for improvement:

- trend reports
  - release and stability testing
  - manufacturing deviations
  - laboratory investigations
  - product complaints
  - environmental monitoring, including facility, utilities, and personnel
  - calibration
  - production trending (yields, waste, reconciliation)
- monitoring (internal and external)
  - supplier performance
  - statistical process control
  - new or revised regulatory requirements
  - changing needs of internal and external customers
  - external benchmarking
- others
  - process improvement to achieve greater efficiency and/or capability
  - implementation of innovative processes and/or equipment
  - response to isolated process or product non-conformances that could impact quality

In addition to these individualized mechanisms, the Product Quality Review (PQR) provides a holistic view of quality performance relative to a specific product or product family on a regular (e.g., annual) basis. This allows management to identify further need for change not apparent when system data is viewed in isolation.

Appropriate, necessary change serves as an indicator of the effectiveness of the other elements of the quality system. Change provides evidence that quality systems are functioning per expectation and attests to an organization's agility and commitment to continuous improvement.

Science-Based Risk Assessment

When assessing a proposed change, the impact of any associated risk should be evaluated using available data. It should be noted that changes are typically made to reduce known risk, rather than increasing known or unknown risk. However, this assessment must be considered as part of the process. It is also important to ensure that a change made in one system will not adversely affect another area of operation. The impact of the change must be evaluated in a holistic manner.

Risk can be assessed using classical tools to identify the hazard(s) associated with each type of risk, the criticality or severity of the potential risk, and the probability of its occurrence to obtain a resulting "risk score." Definition of severity and probability must be predetermined and included in the overall risk assessment. Criteria for acceptance of each potential issue, or the threshold for the "risk score," should be established in advance to determine the overall risk profile for the proposed change.

Changes may be categorized and classified using a risk-based approach. The level of risk includes an assessment of the level of understanding and knowledge of the process and associated inputs and outputs, impact to safety and efficacy, and experience with the execution of similar changes. The process is designed to ensure that the effort associated with making a change is commensurate with the risk associated with the change and the level of product and process understanding. This includes the amount of justification required for the change as well as the approvals required to make it.

This concept of using risk to determine the rigor necessary for individual changes also can be applied to the risk presented by a firm's regulatory change management process. Ideally, firms or sites with low risk due to their application of Q8, Q9, and Q10 should be able to self-manage more changes than those who have not adopted the ICH Quality trio.

Organizational Agility

Organizational agility represents an organization's ability to respond to the need for change. Changes are driven by regulators, business needs, and product and process improvements. The ability of an organization to both quickly and effectively respond to these stimuli will be an important factor toward its success in meeting the needs of all customers, internal and external, including patients and regulators.

In the context of a change management system, organizational agility refers to the ability of the organization to quickly, yet effectively, implement changes. The system design allows for flexibility by specifying the scope of included changes as well as empowering individuals throughout the organization to make changes that have proven to have no impact on the quality of the product or process. An example of this is found in the application of Quality by Design. In a design space environment, stimuli for change may present themselves from one batch to the next or within a batch, perhaps resulting from differences in the attributes of raw materials or data from in-process testing (on, at or off-line). The change management system must be designed to allow rapid responsiveness to these multivariate inputs.

Design space defines relationships and boundaries that have been demonstrated experimentally. Therefore, the need for additional assessment within the design space as would

typically occur in a change management process prior to implementation is absent. The only requirement should be second party verification that the appropriate response was selected; much the same as manufacturing equipment settings are verified for products with traditional boundaries and regulatory applications. Therefore, it is essential that batch records reflect the matrix of interrelationships and the related acceptable ranges for process parameters. Only when a firm proposes to exceed the boundaries of the established design space should the formal change management process need to be invoked, which may include review and approval by health authorities.

An aspect of organizational agility not yet addressed is the ability to manage changes not only within the firm, but at external contractors. As supply chains become increasingly dependent on contractors to meet demand needs, it is essential that change management accommodate this extension of the operation. Since the product owner bears the ultimate responsibility for integrity of the product, regardless of where manufactured, it is vital they maintain visibility to proposed changes with potential impact on the product. This is most readily accomplished through the requirement for a product owner's approval of any changes that may impact product quality or regulatory registrations. The quality agreement with the contractor should include a provision to require review and approval of these changes prior to implementation. The product owner shall bear final responsibility for assessing the impact of the proposed change on the filed process and product quality. A mechanism should be established to provide the product owner with periodic status updates on open changes affecting their products. On an annual basis, the contractor should provide a summary of all changes made to the product, which may be accomplished through an annual document (e.g., the PQR) or as established in the quality agreement.

People agility is an important element that impacts a firm's effectiveness in implementing change. Employees themselves must be managed within the change management system, ensuring that effective, relevant, and recordable training is provided.

Organizational agility is a contributing factor that will allow a firm to self-manage changes in a timely and controlled manner, promoting rapid continuous improvement and reducing risk.

Communication

Ongoing success of change management is dependent on clear and timely communication to all stakeholders. As changes are proposed, feedback from parties that will be impacted by the change must be evaluated to ensure that the change will have the desired effect. Key to these discussions is an agreement on the timeline and steps needed to achieve approval and implementation. In the future, the few changes that must be approved by health authorities, particularly complex ones, may benefit from an early discussion with regulators regarding expectations and timing. The more relevant information that is shared about a change in advance with impacted parties, the more smoothly the approval and implementation should prove.

Management Oversight of Change Management Performance

It is the role of senior management to ensure the existence of a sustainable and effective change management system. Management sponsors the initial design of a robust program and once implemented, uses a variety of tools and techniques to measure the effectiveness of the various stages of the process. There are three indicators which can effectively summarize the health of a change management system, specifically: timeliness, quality (degree of "right first time" performance), and post-implementation verification.

In an effective change management process, changes are implemented in a timely way that meets the needs of the specific situation. Certain changes will require greater urgency than others, but all should be progressed through the process so due dates are consistently met. Management has two responsibilities in this area. The first is to monitor the timeliness of the change management system using appropriate metrics and take corrective action, as needed. The second is to ensure adequate oversight of changes that have been delayed exists in order to understand and mitigate any risk introduced by these delays. In such cases, the potential impact on product quality, patient safety, and customer satisfaction should be assessed, documented, and addressed.

The second key indicator of the change management process is the "right first time" metric. At each critical stage of the process, there is a review and approval gate. A measure of the number and frequency of submissions that are denied approval or require rework is a key indicator of effectiveness. Rejection or rework not only results in costly waste of resources and time, but also may point to deficiencies in other processes, such as training, clarity of requirements, or an inability to appropriately assess and mitigate risk. Management has the responsibility to monitor the right first time metrics of the change process and take necessary corrective action.

The third key indicator is post-implementation verification that changes have been effective in achieving the desired outcome (including no unintended consequences). If the appropriate end state has not been successfully reached in the expected timeframe, an assessment should be completed to understand why this has occurred. Additional work may be necessary, either in the form of revision to the change control or in resolving roadblocks that may be impeding progress. Management should ensure the results of the verification step are trended and that any necessary improvements are made to the overall change management process.

Each of the three indicators described above and their associated metrics are staples of a firm's management review process. Targets should be established for these key indicators and action taken if the desired performance is not achieved. This may include redesigning the overall system if it is not functioning efficiently, providing training to users, addressing specific issues that arise or assessing if the resources allocated to change management are appropriate. The management

review also provides a forum for developing continuous improvement initiatives for a change management process that is already performing within expectations.

Fundamentally, management oversight of the design and execution of change management results in a self-sustaining process which will control change, mitigate any associated risks and allow for rapid improvement to processes and products.

Synergistic Benefits of the ICH Quality Trio

By applying ICH Q8, Q9, and Q10 in the context of change management, the firm or site is able to:

- Control the change process.
- Identify the need for change.
- Accurately assess the risk of the change and correlate it with the effort required.
- Rapidly implement needed change.
- Continuously improve systems, processes, and change management itself.

This purposeful and cohesive approach may allow a firm to be viewed by health authorities as "low risk" and enable greater self-management of changes that today must receive prior regulatory approval.

The use of risk-based change management is a well-accepted concept. In fact, "Pharmaceutical GMPs for the 21st Century – A Risk-Based Approach" (September 2004)[1] states, "Decisions on postmarket changes need to be made based on an understanding of the process and risks associated with the changes on the quality of the manufactured product." The application of risk for changes affecting US-marketed products was further clarified in the FDA Guidance for Industry, "CMC Postapproval Manufacturing Changes Reportable in Annual Reports" (June 2010)[2], which provided a list of changes considered to be "very low risk" and that do not need to be submitted in supplements. Certainly the firm's ability to understand its processes, mitigate risks, and control the change process are factors in assessing the overall risk of a change.

Recently, FDA sponsored a research assessment[3] to determine if a comparability protocol can satisfy FDA's expectations for a specific type of change while enhancing the efficiency of the change process. It was found that the use of an approved comparability protocol is feasible for making a change from one sterile manufacturing site to another under current FDA regulations. Given the potential significance and impact to patient of a change in sterile manufacturing site, the self-management of other, lower risk changes by firms deemed to be capable seems to be a concept worth considering.

The FDA is not alone in their application of risk in assessing changes. Commission Regulation (EC) 1234/2008[4], which became effective in January 2010, describes a system in which certain minor variations can be reported and implemented without prior approval for centralized marketing authorizations in the EU. This change was made "to enable competent authorities to focus on those variations that have a genuine impact on quality, safety, or efficacy."

It is clear that health authorities accept that risk can be differentiated based on the type of change and the controls in place to manage it. The adoption of ICH Q8, Q9, and Q10 as a comprehensive approach reduces the risk of the firm or site's change management process. The proposal described in this article adds an assessment of the firm to the assessment of the change when defining the total risk of the change.

Industry and Health Authority Responsibilities

In this scenario, industry would be required to demonstrate that their application of Q8, Q9, and Q10 reduces the risk of change. This could be accomplished during routine inspections or via inspections for this specific purpose. All documentation pertinent to changes would be available for review by health authorities during inspections, providing regulators the opportunity to verify that the firm has appropriate and effective systems in place for self-management of these changes.

Health authorities would need to agree upon a globally accepted criteria for "low risk" change management systems. In addition, an evaluation would need to be made if the concept herein proposed is feasible under existing global regulations. Firms and/or sites would need to be assessed for risk categorization and routinely evaluated to update the original classification. Again, this could be achieved during routine inspections.

In addition, changes that under no circumstances could be included in such a program, i.e., always require prior approval, should be delineated.

Conclusion

Numerous benefits would result from the adoption of a regulatory change management system that permits self-management of certain changes by firms or sites deemed to be "low risk" based on their implementation of ICH Q8, Q9 and Q10. These include the acceleration of innovation and continuous improvement of product quality; increased adoption of the principles in the ICH Quality trio; more efficient use of health authority and industry resources, focused on higher risk areas; reduced complexity and cost in the supply chain; ensured conformance in all markets and the enhanced ability to supply needed medicines to patients. It is hoped that this article will stimulate the necessary dialogue amongst industry and regulators to establish the baseline criteria to achieve a system in which the majority of changes can be self-managed globally within the framework of ICH Q8, Q9, and Q10 with total visibility to the health authorities upon request.

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This article presents an innovative approach to the completion of Performance Qualification (PQ).

Continuous Verification – Providing an Alternative Approach to Process Validation

by Richard Kettlewell, John Upfield, Rosemary Leak, and Andrew Harris

Introduction

Regulatory authorities around the globe recognize the need for process validation to assure that the production of medicinal products is capable of consistently delivering the required quality.

Recent developments in the pharmaceutical industry driven by ICH guidelines Q8, Q9 and Q10, FDA and EMA draft documents on process validation and an ASTM Standard on Continuous Quality Verification, have created an environment where scientific and technical understanding of products and processes permits innovative, science and risk-based approach to the process validation lifecycle.[1,2,3,4]

Process understanding, together with control of critical quality attributes and critical process parameters, provides the basis for this approach. This provides greater confidence to the company and regulatory authorities that products and processes are controlled, while providing greater flexibility to the manufacturer in the way processes are validated. Continuous verification is initiated before the manufacture of Phase III Clinical Trial batches and continues throughout the product lifecycle, facilitating continual improvement of the manufacturing process.

This has enabled the development of a comprehensive and innovative validation and regulatory package supporting the recent launch of Votrient™ Tablets, based on the use of development, clinical, and commercial batches to verify the performance of the control strategy. The validation approach was reviewed during Pre-Approval Inspection of the drug product manufacturing site, conducted by FDA, EMA, and MHRA. The agencies were fully supportive of the approach.

This change in emphasis has driven a change in thinking about what constitutes validation, leading to many papers and conferences on what validation is and how it may be conducted. Recent articles in *Pharmaceutical Engineering* indicate that regulators, consensus standard organizations and manufacturers are embracing the opportunity to promote and use alternative, science and risk-based approaches to validation.[5,6]

Fundamentally, the actual process of "validating" a product and getting it to market has not changed. It is still expected that 1. validation exercises are governed by a plan, 2. pre-approved protocols define the scope of work to be undertaken and acceptance criteria, 3. approaches are justified, 4. aspects of qualification are reported, and 5. the overall validation exercise is concluded by a summary report.

However, while the basic deliverables may remain the same, the opportunity to utilize greater scientific understanding in the design of validation programs is welcomed and should be embraced for those products and processes developed following a Quality by Design approach. **An increase in the scientific and technical content of the overall process validation provides better opportunities to justify "what is," and sometimes more importantly, "what is not" validated, and the scope and extent of validation work undertaken.**

There is much made of changes of terminology, but fundamentally the validation of a product/process should be viewed as a lifecycle – the Process Validation Lifecycle. The recent draft guidance issued by FDA illustrates this as a three stage process:

- **Stage 1, Process Design** – the stage at which product and process understanding is developed. At its basic level, this delivers a list of Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) that form the basis of ongoing process control.

It is proposed in this article that from the time a draft control strategy is identified, typically for Phase III Clinical Trial batch manufacture, then verification of process control may be commenced. This will initiate the process validation activity providing the assurance that product of the requisite quality is being produced.

- **Stage 2, Process Qualification** – a multi-component activity concerned with the qualification of facilities and equipment, the validation of analytical methods and taking the process to a point where it may be commercialized.
- **Stage 3, Continued Process Verification** – ongoing verification that ensures the production process remains in control and continual improvement is facilitated.

The end of Stage 2 is the point at which the manufacturer is able to document that the process is capable of producing material of the requisite quality to be commercialized.

Traditionally, this Performance Qualification (PQ) has involved the production of three consecutive, commercial scale batches, which have been documented as meeting acceptance criteria. The successful completion of these three batches indicates that the process is controlled and supports the release and supply of commercial product.

While this approach remains as a viable option, there is now the opportunity to investigate improved strategies for achieving the point of commercialization. These have the potential to offer significant benefit to manufacturers and regulators alike.

A comparison of traditional and 'Continuous Verification' (CV) approaches to performance qualification is shown in Table A.

Traditional Approach	Continuous Verification Approach
Validation status based largely on data from three batches	Validation based on development knowledge and on-going commercial performance confirmed on every batch
Relies on increased sampling rate for PQ batches	Potentially employs continuous measurements on every batch produced
Performance Qualification criteria applied to three targeted batches	Performance Qualification criteria applied to all batches
Knowledge from data trending is separate from the validation exercise	Data trending is an integral part of the approach
Re-validation is required to support change	Scientific knowledge and risk assessment reduce the need for discrete re-validation exercises
Provides assurance of process performance at point of commercialization	Provides assurance of process performance through the product lifecycle

Table A. Comparison of process validation approaches.

For a recently launched product, a CV approach, incorporating data and knowledge from manufacture of development, clinical, and commercial material, has been used as an alternative to the traditional approach of verifying three commercial scale batches. For this product, this approach enabled the provision of a comprehensive package of data supporting process validation based mainly on clinical production, and requiring only one batch of commercial material to be manufactured.

The validation approach was reviewed during Pre-Approval Inspection of the drug product manufacturing site, conducted by representatives of FDA, EMA, and MHRA. The agencies were fully supportive of the approach. Additionally, details of the validation approach have been provided with the submission in many international territories. Although some questions for clarification have been asked, there have so far been no adverse comments about the CV approach with no agencies asking for traditional validation to be undertaken.

The product has recently received approval in the US, EU, and a number of other markets.

What is Continuous Verification?

Continuous Verification (CV) is a systematic, science and risk-based approach to verify and demonstrate that a process operates in such a way that it consistently produces material which meets the predetermined CQAs, both at the time of commercialization and through the lifetime of the commercial production process.

Adopting a CV approach to performance qualification allows batches made during development to the intended commercial formulation and process, i.e., within the intended design space, to be included in the validation exercise. These batches may be manufactured in the center of the intended design space or at other positions in the design space, using the control strategy, including control of the CQAs and CPPs, anticipated for future file. The batches are most likely intended for clinical use (e.g., for Phase III Clinical Trial studies) or for stability testing to support submissions. The data from these batches are used to verify the process. This approach means that process validation is considered much earlier in the product development lifecycle, enabling key information to be collated and reported in support of the validation exercise.

New knowledge from these batches or from other development work may indicate that a change in the control strategy is required. Depending on the significance of the change, there may be a gap created in the data available to support validation. If this is the case, the gap is risk-assessed to determine what mitigation is required. For example, if development batches are manufactured to support the change, these could be incorporated into the validation program.

Before PQ is complete and commercial product is released, any differences between batches used in the PQ program thus far and the commercial product are risk-assessed to identify whether any further data are required. Scientific understanding may fully support that a difference (for example, the image

for clinical batches may be different from commercial batches) presents no risk to the control of the commercial product and that no additional data are required. These differences may be discussed at pre-submission meetings (e.g., pre-NDA or equivalent meetings) and are transparent to regulators at Pre-Approval Inspection (PAI).

This approach to validation enables continual improvement of the control strategy during development to be included in validation of the product and provides high confidence that the product will be well controlled. This philosophy of enabling continual improvement of the control strategy through a risk-based scientific approach continues throughout the lifecycle of the product.

To achieve the inclusion of development data in PQ, the Validation Master Plan is issued before Phase III Clinical Trial batches are made and when the draft control strategy is identified.

Protocols containing acceptance criteria with supporting rationale are written for each campaign of clinical and commercial batches included in the PQ for commercial launch. Data are reviewed and trended for each batch and for each campaign to show compliance with the PQ criteria. Prior to commercialization, a validation summary report is written, drawing on previous PQ campaign reports to show compliance with criteria and completion of the validation plan.

From launch onward, data are reviewed on a batch and campaign basis. An essential part of CV is that relevant attributes of the input, intermediate and drug product materials, and manufacturing process parameters are monitored and evaluated, both within and between batches, as part of routine operation. While some elements of a traditional periodic product review are carried out under CV on a batch-by-batch basis, other elements of the review process, e.g., reviews of CAPAs and customer complaints continue to be required on a periodic basis. These formal periodic reviews are undertaken to determine the need for any changes in manufacturing, control procedures, and/or product specifications, including any changes to the design space, control strategy, and models for the product. The frequency of the periodic review will depend on the number of batches produced within a specific timeframe and may vary during the product lifecycle.

CV approaches to process validation provide greater assurance of product quality at the point of commercialization and through the lifecycle by:

- enabling ongoing assessment and knowledge to be built into the validation exercise, providing a lower risk approach to the point of commercialization
- trending of critical aspects through clinical, development, and commercial manufacture
- verifying that any multivariate relationships between attributes and parameters found in development are maintained in commercial production
- enabling verification of the design space
- using a data set from a larger number of batches
- potentially influencing the development plan and the way in which batch data are analyzed to support CV
- supporting change control, continual improvement, and knowledge management

This CV approach is applicable to new products that have been developed following a Quality by Design approach. In addition, aspects of CV also may be applied to products developed under QbD, but validated for commercial supply using a traditional approach. This may be achieved by trending and ongoing batch-by-batch assessment in commercial production enabling knowledge management and continual improvement.

Practical Application of CV for a New Product

Introduction

Votrient™ Tablets for the treatment of renal cell carcinoma are immediate release, film coated tablets for oral administration containing either 200 mg or 400 mg of pazopanib free base as the hydrochloride salt. A common granule and compression blend are used for both tablet strengths. The process employs Process Analytical Technology (PAT), including in-line Near Infra Red (NIR) spectrometry and multivariate models with real time release of the drug product. Figure 1 provides a high-level overview of the CV approach adopted for Votrient™ Tablets. This approach was shared with FDA at two meetings, and discussed with the PAT team in the EU and with several international regulatory agencies.

The terms Performance Qualification 1 (PQ1) to represent the body of work achieving the point of commercialization, Performance Qualification 2 (PQ2) to describe a period of verification post commercialization, and "on-going verification" to describe verification through the lifetime of the drug product were adopted. Similar terminology is well established within the pharmaceutical industry in connection with the validation of quality water systems. The following sections provide an overview of the approach taken for the process validation of Votrient™ Tablets.

Validation Planning and Prerequisites for PQ1

The validation lifecycle adopted for Votrient™ Tablets was described in a Validation Master Plan (VMP), detailing the objective, validation approach, brief product development history, and process description.

Potential CQAs and associated CPPs were identified and documented within Stage 1 "Process Design," and were then verified on an ongoing basis during the manufacture of development and clinical campaigns. For this reason, an essential component of the proposal to adopt CV within the drug product validation lifecycle was the generation of the VMP earlier in the product development lifecycle. This allowed the VMP for the drug product to incorporate development learning and include continuous verification of the clinical batches as part of the approach to PQ1 and PQ2.

As the development program progressed and more information became available, the VMP was updated to include more details of the final validation approach to be adopted.

This included the generation of a specific PQ1 validation rationale detailing the reasons behind the strategy adopted and a PQ1 validation protocol detailing the number of batches and acceptance criteria which were to be applied to the PQ exercise.

The CV approach is equally applicable to drug substance and drug product, but in the case of Votrient™ drug substance, a more traditional approach to process validation using three conformance batches was adopted based on previously agreed project schedules.

Although different validation strategies were adopted to achieve the point of commercialization for the drug substance and drug product, the same underlying levels of product and process understanding were available. This facilitated the adoption of CV concepts for the drug substance post commercialization.

What Were the Pre-Requisites for PQ1?

Before commencing PQ1, sufficient knowledge and understanding of the commercial product and process were required. The following were identified as pre-requisites:

- qualification of all related facilities, equipment, and process measurement technology
- identification of potential CQAs and CPPs
- identification of a control strategy and associated design space
- definition of specifications for drug substance and drug product
- documentation of the scientific basis for the above
- documented risk assessments to provide assurance that product and process risks had been identified and managed

This enabled identification of PQ1 process performance criteria as:

- CQAs met and trended
- CPPs measured, monitored, controlled within their required ranges, and trended
- unit operation end points controlled, and where appropriate, monitored and trended
- multivariate relationships monitored and trended

How Were the Pre-Requisites for PQ1 Achieved?

Early development work using commercial scale equipment at the proposed commercial manufacturing site allowed the identification of process parameters and material attributes relevant to drug product performance and enabled the description of the process for the commercial scale manufacture of Votrient™ Tablets.

Further commercial scale work provided an understanding of the relationships between attributes of API, attributes of in-process materials produced from unit operations (e.g.,

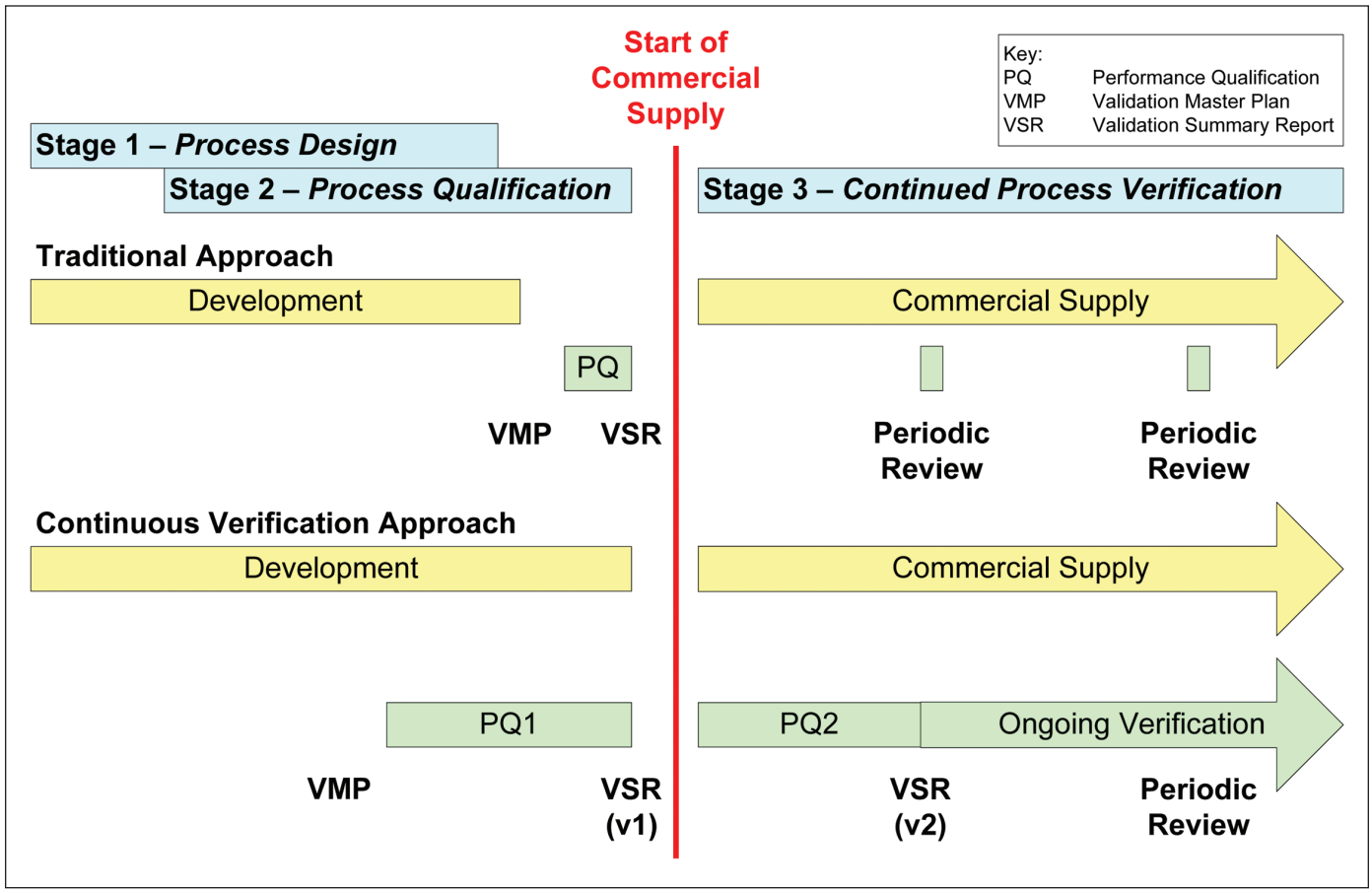

Figure 1. Illustration of validation approach adopted for Votrient™ Tablets.

granule properties), processing parameters and critical quality attributes of the drug product. It indicated those process parameters, and material attributes which were critical to control to achieve the drug product CQAs, and enabled the definition of the process and the draft control strategy for the commercial scale manufacture of Votrient™ Tablets.

Following risk assessment to prioritize activities, further development work to establish the design space and final control strategy for the commercial manufacture of Votrient™ Tablets was undertaken. This work used a Design of Experiments with extremes of processing parameters and stretching of excipient attributes to demonstrate areas of acceptable process performance at commercial scale and confirm earlier development conclusions. This completed the pre-requisites for PQ1.

Drug Product PQ1

In order to use data from the clinical trial batches, the "pre-campaign protocol" was introduced for each manufacturing campaign. This pre-approved document detailed the batches to be manufactured, the formulation, the control strategy, the process performance criteria, the specification to be applied, the status of analytical method validation and details of any development work to be undertaken. The output of each campaign was formally reported against the pre-campaign protocol ensuring knowledge was available to support the process validation. This approach to the collation of information was cited as a good practice during the Pre-Approval Inspection.

As this product had a high demand for clinical material, a total of 31 clinical-image batches (1 × 200 mg and 30 × 400 mg) and one commercial image 200 mg batch, all at commercial scale, were manufactured prior to launch using the defined control strategy, within the design space intended for commercial production. A comparison of clinical and commercial tablet images is given in Table B. Part of the validation rationale included a scientific and technical appraisal of 200 mg and 400 mg tablet production in both clinical and commercial images. **An understanding of the relationships between tablet strength, shape, porosity, thickness, disintegration time, and dissolution rate provided the rationale for using data from one strength/image to support other variants.**

These 32 batches comprised the PQ1 validation batches and were documented within the PQ rationale and PQ protocol.

	Clinical		Commercial	
Strength (mg as free base)	200	400	200	400
Tablet Core Formulation	Commercial Formulation			
Tablet Shape	Oval Shaped	Oval Shaped	Modified Capsule Shaped	Modified Capsule Shaped
Film Coat Color	White	White	Gray	Yellow
Debossing	None	None	Debossed on one face	Debossed on one face

Table B. Comparison of clinical and commercial tablet images.

Batch process data and end product testing data were assessed against the process performance criteria to demonstrate that the process provided product of acceptable quality. Data from the exercise were added to univariate and multivariate statistical charts for comparison purposes. Control charts with action limits were developed once sufficient data had been produced.

The PQ1 batches provided evidence that the process performed reliably and delivered product of the desired quality and in accordance with the process performance criteria. The PQ1 batches were reported, making reference to conformance with batch release methods, supporting development history, and supporting facility and equipment validation status. This report is the first version of the Validation Summary Report (VSRv1), and its issue marked the completion of PQ1.

Approval for Commercial Supply

In order to approve the start of commercial supply, the following were in place and documented for Votrient™ Tablets:

- the process for CV
- qualification of all equipment and systems prior to use in PQ
- a validation master plan, validation rationale, and validation protocol detailing the approach to performance qualification and the criteria that must be met in order to consider the process qualified
- process control strategy and design space, including requirements for ongoing monitoring and trending of data
- product and process understanding supporting the control strategy and design space
- verification that the control strategy enables consistent manufacture of product complying with its CQAs
- batch data from PQ1 batches showing compliance with the process control strategy, process performance criteria, end product specifications, and GMP
- risk assessment and risk management plan
- an approved report of the work undertaken at PQ1

Satisfactory completion of the review of the above, and approval of VSRv1 represented internal approval to commence commercial supply.

Drug Product PQ2

The Validation Master Plan described a second stage of CV to confirm that variation inherent in routine manufacturing operations is managed by the control strategy, and to gain further knowledge and understanding of the process.

In determining the extent of this stage, consideration was given to the number of batches and the timeframe over which they were to be manufactured to encompass variation in, for example, input materials, personnel shift patterns and climatic conditions.

For Votrient™ Tablets, this stage will comprise review of 10 commercial scale batches (representing one year's clinical and commercial production). The following will be reviewed:

- verification that the control strategy enables consistent manufacture of product complying with its CQAs
- Batch data from PQ2 batches showing compliance with the process control strategy, process performance criteria, end product specifications, and GMP
- review and verification of models used in the control strategy (e.g., NIR)
- risk assessment and risk management plan
- an approved report of the work undertaken at PQ2

At this point, a final validation summary report (VSRv2) will be produced, marking the end of PQ2 and completion of the work described in the Validation Master Plan.

Continuous Verification Throughout Lifetime of the Drug Product

As each batch is manufactured, it will be verified that the batch has been produced in accordance with the control strategy and within the design space, and that the process performance criteria, including trending requirements, have been met. In addition, periodic product reviews will be undertaken.

Impact on Quality Systems

The introduction of new ways of working impacted to a greater, or lesser extent, a number of Quality Systems and Standard Operating Procedures –notably those related to batch release, change management, deviation management, periodic review, and risk management.

Batch Release

Existing batch release procedures were modified to include verification that a batch has been produced within the design space and in accordance with the control strategy, and that the process performance criteria have been met.

Change Management

All planned changes which have the potential to impact the quality of a material or product will be prospectively assessed in order to ensure that the risks associated with the implementation of the change are identified, quantified, and managed.

A risk assessment will be carried out to determine the level of re-qualification required. If the changes proposed are within the design space, the changes will be managed through internal quality systems, as it has already been shown that there will be no impact to the CQAs.

If the changes proposed are beyond the boundaries of the known design space, then after technical justification and internal approval, appropriate regulatory action will be taken prior to making this change.

Existing product and process knowledge and ongoing verification will be used to support all changes.

Deviation Management

The implementation of a CV approach meant that a number of potential failure modes needed to be considered in detail; for example, failure of PAT equipment. A number of decision trees were developed to identify the actions to be taken in the event of these failures occurring. For example, the failure of a NIR end point control on blending may result in the control of blending by the use of fixed time rather than direct measurement of homogeneity as the relationship between blending time and homogeneity is understood from development work performed.

Periodic Review

The periodic product review process has been modified to ensure that the design space, control strategy, and models are included in the review.

Risk Management and Continual Improvement

As part of the product lifecycle management and CV approach, risk assessments are carried out on a regular basis, including at the end of PQ1 and the end of PQ2, and periodically during subsequent routine manufacture. Depending on the stage in the product lifecycle, the outputs from the risk assessments are incorporated into development plans or into continual improvement plans in routine manufacture.

CV: Benefits Achieved

The traditional "three batch" approach to process validation adopted by industry and regulators provides little opportunity to apply risk-based scientific rationale to PQ.

CV provides a viable alternative to the "three batch" approach and importantly has the potential to use the knowledge from development and clinical trial batches to support the overall Process Validation lifecycle. This flexibility of approach offers the following potential benefits:

Greater use of Development Data to Support Commercialization

The manufacture of development and clinical material is clearly a pre-requisite for the commercial launch of a new pharmaceutical product. The use of data from these exercises effectively increases the population of data available to support the point of commercialization and ongoing commercial manufacture. This approach has the advantage of:

- moving the focus of validation from three batches to a larger number of batches manufactured mainly for clinical and development purposes
- promoting more effective use of product and process knowledge to ensure process robustness post-commercialization
- using product knowledge to promote scientifically justified validation rationales, for example, the CV approach for the Votrient™ Tablets 200 mg strength was supported by the scientific understanding of the relationships between the attributes and manufacturing processes for 200 mg and 400 mg strengths of tablets and between the clinical trial and commercial image, without the need for including the manufacture of three replicate batches of the 200 mg commercial image.

Flexibility in the Validation Approach Taken to Achieve Commercialization

By issuing a validation plan earlier in the development process and stating the intention to use data from development and clinical campaigns to support the point of commercialization, greater flexibility in the final approach to validation is introduced. In the Votrient™ Tablet example, the CV approach supported the manufacture of only one commercial image batch of tablets to achieve commercialization. For a low off-take product, this avoided the risk of material write-off (due to limited shelf life) and all associated costs.

Improving Operational Quality

It also would be expected that adopting a CV approach to PQ could lead to the following benefits:

- Fewer deviations – the increased level of process understanding obtained from a larger population of batches prior to commercialization presents opportunities to address start-up issues of a new process.
- More relevant process performance criteria – relevant to the product, rather than generic, being derived from process understanding. This increases the confidence that the meaningful attributes and parameters are being measured to track quality and that effort is not expended on collecting and reviewing large volumes of data of little relevance.
- Increased trending and assessment of data – presents the opportunity for early identification of atypical trends before quality issues arise, both within a batch and between batches.
- Fewer batches to reach the point of commercialization – while the "Three-batch" approach was used for the pazopanib drug substance, a retrospective analysis of the campaigns used to develop and commercialize the drug substance indicate that point of commercialization may have been claimed 11 months earlier with the manufacture of fewer batches.
- Reduced operational costs – derived from the above benefits.

Approach to Quality and Risk Management

The closer link between development activity and clinical and commercial supply has provided improved levels of knowledge transfer, giving the following benefits:

- More efficient and effective change control – changes proposed can be assessed against the available process understanding, minimizing the level of additional verification required to support the change.

A future aim will be to incorporate additional knowledge in regulatory filings to facilitate certain lifecycle changes post-approval, effectively reducing the number of regulatory post-approval changes.

Conclusion

This article describes our first application of CV to the process validation of a pharmaceutical drug product. While much can be taken from the experience of developing and filing Votrient™ Tablets, it is intended to further investigate and develop these concepts.

Future efforts will be aimed at making greater use of small scale batches, and incorporation of other variables within the Design of Experiments to provide greater manufacturing and regulatory filing flexibility, e.g., influence of differing site of manufacture, and changes in equipment type.

Clearly, each product will require different approaches to the number and scale of development/clinical batches required, so no single approach to the use of CV can be described. However, the principle of using late stage development and clinical data to support the commercialization of products is flexible and this flexibility is being used in a number of pipeline products. What is clear though is that "validation" is no longer about a number of batches, but more about the accumulated product and process understanding.

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Risk Management – A Key Requirement for Project Success

by Brett Schroeder, John Alkemade, and Gordon Lawrence

This article discusses how risk management can aid in project success. It looks at the potential gain from good risk management, examines some typical risks that recur regularly on projects, and offers a suggested methodology for managing project risks.

Introduction

Most people involved in capital investment project execution are aware of the link between early design definition and project success. However, the positive role of good risk management is not always as well known. This article discusses how risk management can aid in project success. It looks at the potential gain from good risk management, examines some typical risks that recur regularly on projects, and offers a suggested flow scheme and methodology for managing project risks.

The Next Step after Considering Good Design Definition

Over the course of our work in recent years, we have observed that a high percentage of major capital projects fail to meet their project performance targets.[1] This failure can very often be traced back to poor early design development. Indeed, the link between good early design development and project success has been demonstrated in numerous articles over several years now.

Several organizations provide either qualitative or quantitative measures of early design development. For example, the Association for the Advancement of Cost Engineering-International (AACE-I) provides a qualitative measure[2] and other, quantitative measures exist, such as the "Project Readiness Index."[3] All these sources generally give a similar description of what level of design definition is required in order to achieve a cost estimate of a particular level of accuracy. They generally include an assessment of the level of completeness of such aspects as: scope definition, engineering documents, team alignment, and project control systems.

However, poor design development does not explain everything in relation to the failed projects. Figure 1 shows the Project Readiness Indices of a dataset of capital projects,[4] mapped against their level of cost overrun/underrun of the approved budget. The graph unsurprisingly illustrates that a better level of Project Readiness Index correlates with lower levels of cost overrun. However, as circled in red in Figure 2, the graph shows a number of outliers which had a significant cost overrun irrespective of their level of Project Readiness.

These outlier projects were examined in order to try to ascertain whether there were common characteristics in this sub-group. The common denominator among all the projects in this sub-group of outliers was that each lacked a clear strategy for documenting potential project risks and mitigating those risks.

Therefore, it was decided to focus on understanding more about the identification and mitigation of risks with the eventual objective of developing a tool to address "Risk Identification and Management."

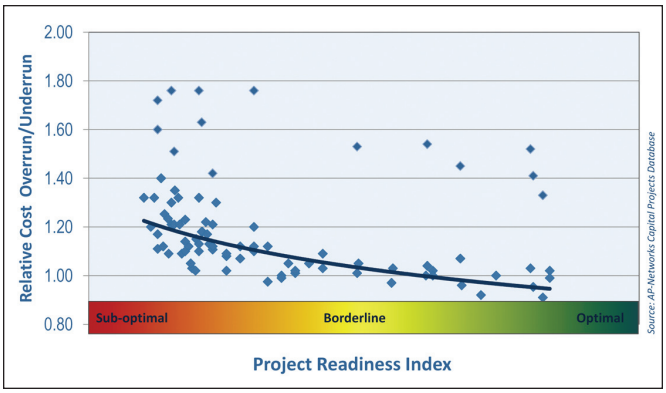

Figure 1. Better levels of project readiness index are correlated with reduced levels of cost overrun.

The Need for Risk Management

Among the projects in the dataset, significant risks were not being identified and managed. Risk management, if it occurred at all, was an

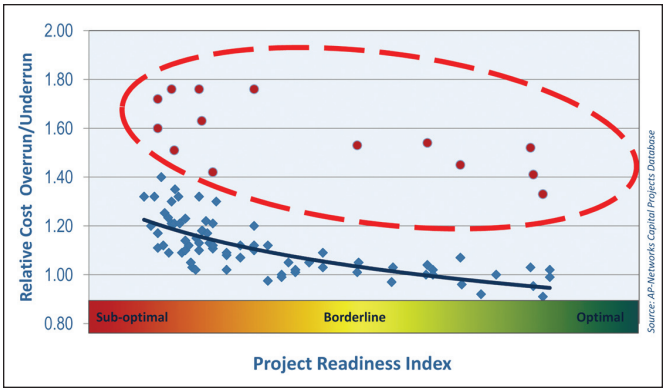

Figure 2. Lack of a risk management strategy correlates with the outliers from the readiness index.

ad-hoc exercise, with spreadsheets littered all over the organization – lacking consistency in categorizing and prioritizing risks. Furthermore, there was no clear assigning of ownership for action/response plans. There tended to be no standardized process for regular management review. This meant that risk occurrences and hence potential lessons learned were not being passed on to other project teams. As a consequence, the organizations were not achieving optimum performance, and were exposing themselves to unnecessary liabilities.

A literature search revealed that other studies had come to similar conclusions. For example, a study by IBM[5] found a distinct correlation between company success and the presence of formal risk management procedures. Their set of high performing companies had greater return on net assets of (9.3% vs. 7.9%) and a higher compound annual growth rate (18.7% vs. 16%). Thirty-five percent of their outperformers had formal risk identification procedures versus 8% of underperformers and 35% of their outperformers routinely monitored risk factors versus 10% of their underperformers.

Specifically within the pharmaceutical industry, there are risk management tools available; one example being the "Quality Risk Management" Guideline Q9,[6] produced by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[7] However, many of these tools focus heavily on how to design and operate a facility in order to ensure a quality product.[8] They tend not to focus on the more general, engineering or construction related risks such as "What is the risk to the schedule if this equipment item is delivered to the site late?" or "Is there a risk of disrupting existing site operations during construction?" or "Have we recognized all the government permits that are required to build this facility?" or "Is there a risk of miscommunication between the design office and the owner engineering office?"

Defining Risks

Kerzner defines risk as "[a] measure of the probability and consequence of not achieving a defined project goal."[9]

Desired project outcomes are inherently under threat of failure or non-compliance due to events that may occur during the project life-cycle. Such events may vary in their degree of probabilistic occurrence, magnitude of impact (severity), and level of manageability.

For our purposes, a risk can be defined as any uncertainty that if it occurs would affect one or more project objectives negatively. We shall discuss the level of risk exposure as being a function of the probability of the risk occurring and the severity of its effect if it does occur.

Risk mitigation will be taken to mean any action taken to reduce either the probability of occurrence or the severity of the effect of a risk. Contingency planning will refer to plans of what to do once the risk has occurred.

The Risks to be Managed

We then looked through a database of projects[10] again, this time looking for projects that did appear to have a good risk management process, rather than those that clearly didn't.

Some projects had focused only on post startup process operational risks (such as those discussed in Annex II of ICH Guideline Q9) and neglected other risks, such as those associated with project execution during engineering and construction, prior to startup. In general, we found that the better risk management processes looked at risks related to aspects of project execution as well as those related to facility operability.

All in all, from our database of projects, we were able to develop a list of more than 110 "generic" risks that cropped up time and again in the projects that we reviewed.[11] These generic risks could be grouped, as shown in Table A.

Risk Mitigation

Once the risks had been identified, the project teams that had good risk management plans then proceeded with studies to quantify the risk exposure of their project. This was often

Risk Category	Examples
1. Technology	• Ensuring adequate technical definition prior to detailed engineering • Use of new or unproven technology • Design flaws
2. Planning/Schedule	• Permitting takes longer than anticipated • Long lead times for major equipment
3. Organizational	• Adequate staffing • Effective team integration and interface management • Joint venture partner alignment
4. Market/Commercial (Economic)	• Ensuring Robust Economic case (ROI) • Cost escalation and budget constraints
5. Scope Definition	• Tie-ins with existing facilities (Brownfield modifications) • Adequate understanding of OSBL (Outside Battery Limits) interfaces
6. Procurement and Materials	• Availability of staff and supporting equipment
7. Commissioning and Startup	• Interference with ongoing operations
8. Health, Safety, and Environmental	• Safety incident

Table A. Generic risk areas – rated in order of estimated risk severity.

done using a Monte Carlo style simulation. For all the individual risks, the Risk Severity was calculated (likelihood of occurrence and the level of impact). The Monte Carlo analysis then simulated "random" occurrence and severity of each of the risks in the risk register.

Once teams were aware of the extent of their risk exposure, the teams then proceeded to assess which risks could be mitigated and using tools such as tornado charts, determined the risks with the highest negative contribution (Cost and Duration), thus deciding on which were the most important risks to mitigate.

This then assisted the project teams in deciding the priority of which risks to focus mitigation efforts on and to develop a mitigation plan with the intent to reduce the risk severity (lower the likelihood of occurrence or lower level of impact).

The Potential Gain – Case Study

To illustrate the beneficial effect of this work, below is a case study example of one particular facility. The study shows the risk exposure before (unmitigated) and after (mitigated) mitigation plans had been implemented.

Unmitigated Risks

The outcome of a Monte Carlo analysis, as shown in Figure 3, was a frequency distribution (or S-curve) of the risk exposure. In this example, the unmitigated risk register (i.e., no mitigation planning done) showed an additional cost impact of 75 percent (Probability 50) on top of the current cost estimate and likewise 122 percent on duration.

Mitigation of Risks

Figure 4 shows the results of the risk exposure calculation after the major risks had been mitigated. In this example, the mitigated risk register (i.e., mitigation planning developed and implemented) shows a residual cost impact of 13 percent (Probability 50) on top of the current cost estimate and likewise 19 percent on duration. (Note: These percentages do not reflect additional contingency requirements in the cost estimate for "unknown unknowns" or duration float requirements in the schedule, but represent the quantified risk exposure, which could be translated as management reserves and will only be utilized if one of the risks occurs).

Figure 5 summarizes, by showing a comparison of the risk range, pre and post mitigation. In this particular example,

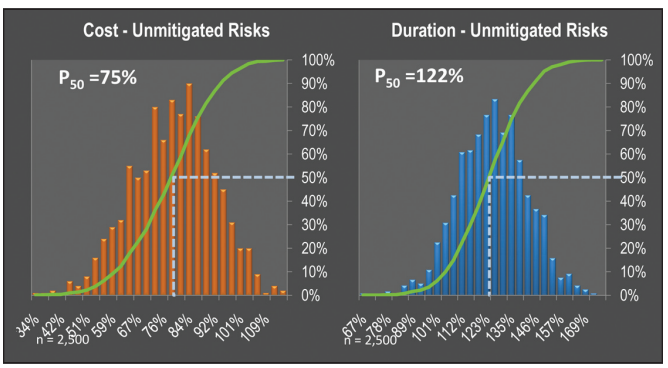

Figure 3. Risk exposure – unmitigated.

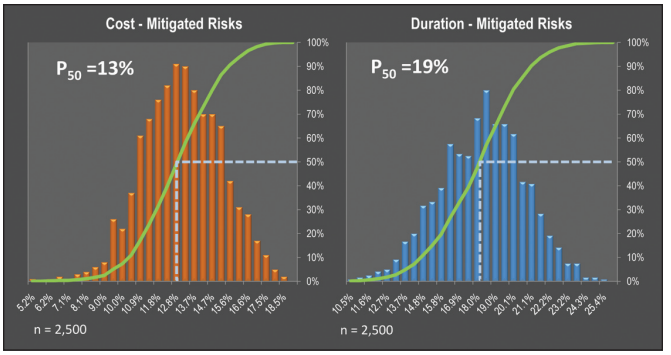

Figure 4. Risk exposure – mitigated.

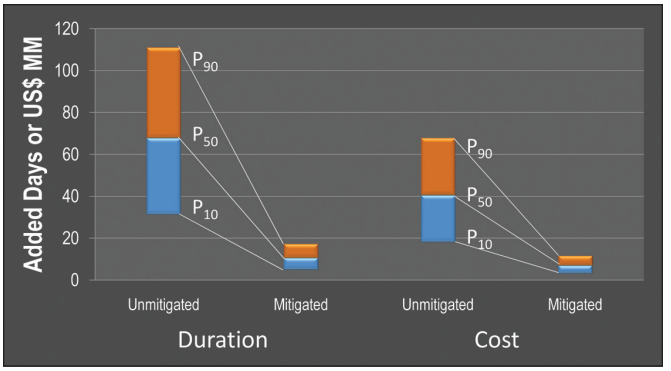

Figure 5. Benefits of quantification.

the reduction in risk around both the cost and the schedule duration is dramatic.

The Prescription for Success

Once we had established the importance of Risk Management, the next step was to develop a "process" of risk management, based on the "good practice" that we observed. The process that we developed is based upon the following key activities.

1. Establish a Common Risk Breakdown Structure (RBS)

Develop a logical structure for grouping risks. A standardized Risk Breakdown Structure (RBS) provides a logical method to group risks. The consistent structure can, in turn help teams analyze risks across a portfolio and facilitate the sharing of risks across different functional areas. When reviewing risks from previous projects, use of a RBS allows teams to learn from experience and better understand the systematic threats that need to be addressed during the (following) risk identification stage. Moreover, teams should be able to identify from the previous projects what action plans were implemented and their level of effectiveness. The structure that we settled on and have now successfully used with a number of capital project teams is shown in Table B.

2. Identify the Risks (Through Cross-Functional Risk Identification Brainstorming Workshops)

Identifying the risks should (at least initially) be done in a large, multidiscipline, "brainstorming" group. In our view, risk identification and assessment workshops have proven

RBS	Examples
Project Location	e.g. availability of local infrastructure, etc.
Market and Commercial Business Issues	e.g. speed to bring to market, etc.
Process Technology	e.g. new technology, etc.
Scope Definition	e.g. availability of site data, etc.
Contracts and Contracting Strategy	e.g. incentive schemes, etc.
Communication Interfaces	e.g. joint venture partners, etc.
Health, Safety, and Environmental	e.g. contractor safety record, etc.
Execution Complexity	e.g. site access constraints, etc.
Validation, Commissioning, and Startup	e.g. handover sequencing, etc.
Operational	e.g. operator training, etc.

Table B. Example RBS.

to be one of the single most important steps within the risk management process. In planning for such workshops specific attention is given to the attendee list, which should reflect the broad spectrum of all project stakeholders. These workshops provide a unique opportunity for team members to not only identify potentially adverse issues arising from their area of responsibility, but also allow these team members to develop and crystallize essential interdependencies among various threats. Hence, risk workshops will add to the connectivity of the individual disciplines and reveal possible misalignment among team members on certain risk expectations. The brainstorming sessions should ask such questions as:

- What can go wrong?
- How can it go wrong?
- What is the potential harm?
- What can be done about it?
- What problems have we experienced in the past?
- How did we manage it when it happened?
- How can we stop it from happening again?
- What losses have our competitors experienced?

We developed a pro-forma for participants to write down their potential risks on. This improves the capture of ideas during the brainstorming. The pro-forma includes space to write: a description of the risk, a check box for affected outcome, a check box for risk severity, and a check box for risk manageability.

It is recommended that several team workshops are held prior to the execution phase. These team workshops may have at times various foci other than risk depending on the project area or discipline under discussion (e.g., planning status, team alignment, etc.), but should at a minimum feature a review or discussion of the current status of risk assessments and risk-related action plans.

3. Quantify Impact Values and Probabilities

Once the risks are identified, the affected outcome needs to be specified. The following are outcome categories that are most commonly used:

- CAPEX cost
- Project Schedule
- Construction Safety
- Facility Operability
- Environmental
- Company Reputation

Next, the level of risk exposure needs to be assessed, by quantifying probability of occurrence and severity if it occurs. To classify severity of occurrence, we use the criteria in Table C. Plotting the risks on a matrix such as the one shown in Figure 6 helps to visualize where the highest risk exposure lies.

4. Document the Risks in a Risk Register

Next, the risks need to be documented in a register that ideally can be accessed by all team members and includes fields for:

- Risk ID and Text Description
- Affected Outcome
- Probability and Severity Ratings
- Level of Manageability
- Risk Owner
- Mitigation Action(s) and Owner
- Contingency Plan(s) and Owner

Among those project teams that are addressing risk management, many teams have adopted spreadsheets to maintain risk registers. There is nothing inherently wrong with the use of spreadsheets, but their use tends to concentrate the risk management process to a single individual and preclude the cross-functional dialogue that should be a key part of the risk process. The use of specialized risk management software systems avoids this problem since the register can be accessed and reviewed by various team members.

5. Develop Mitigation and Contingency Response Plans

Many teams do a good job at identifying and quantifying risks and capturing them in a risk register. However, in our experience many teams fail to complete the risk management cycle by developing the appropriate mitigation and contingency response plans. For large registers the task may appear overwhelming to develop response plans for each risk. If this is the case, the team needs to prioritize on the high-impact and high-probability risks and ensure that at a minimum these are addressed. The team also needs to communicate the low probability risks that have high impact on project objectives. These are the threats that often result in catastrophic failure.

All of this work in developing mitigation and contingency plans does take time and effort. However, this needs to be weighed against the potential loss in terms of cost and schedule if a particular risk is not mitigated and comes to pass.

6. Assigning Responsibilities

The next step in the process requires responsibilities to be

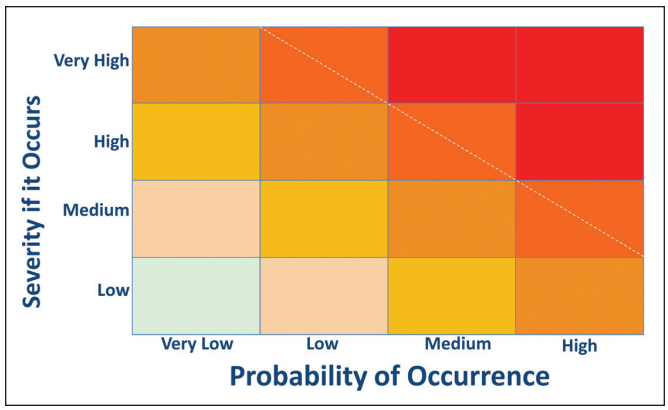

Figure 6. Risk exposure matrix.

assigned in order to ensure that the mitigation plans are implemented and the contingency plans fully prepared. The following are recommended:

- Assigning a Risk Champion/Coordinator with adequate authority to police the activities of those developing mitigation and contingency plans.
- Assigning specific responsibilities for each mitigation and contingency plan preparation.
- Including the development of those plans in the project schedule.
- The mitigation and contingency plan preparations are monitored and reviewed at each project progress meeting.

7. Review the Risk Register as Part of Regular Team Meetings

We recommend making the review of the risk register a regular part of the weekly or monthly team meetings. This ensures that the risk process remains central to the management and communication processes.

8. Re-Evaluate Risks Periodically

Even after the project is well under way, teams still need to hold-periodic cross-functional risk events to update the register with new threats and opportunities and re-assess existing risks.

9. Lessons Learned

In addition, it is helpful to conduct project closeout assessments of the efficacy of specific risk mitigation actions taken during the project. The results of such feedback measures strengthen the use of "lessons learned" in future projects.

A Risk Management Tool

Based on the process described above, a Web-based tool was developed for Risk Analysis and Management. This tool has been used successfully on a wide range and large number of projects in the last four years. The tool allows teams to: identify, evaluate, and register risks and key information; assess risk severity/manageability; track risks and mitigation plans; access to datasets of most common industry risks; and share risk information

The tool can be used by all team members with minimal training. It provides a framework for carrying out the activities discussed in the previous section and it offers the team a number of visual reporting formats (such as spider charts) to illustrate risk severity, track risk mitigation and contingency actions, and so forth.

Conclusion

Achieving project success requires not just good front end definition and a well integrated project team. Project success also hinges on good management of project risks. This requires teams to:

- identify, evaluate, and register risks and key information
- assess risk severity/manageability
- develop mitigation and contingency plans
- actively track the risks and mitigation plans

Holding a risk identification session early in a project, as part of the front end development process will improve the project teams chances of having a successful project.

Definitions		**Affected Outcome**					
		CAPE X	*Schedule*	*Safety*	*Operability*	*Environmental*	*Reputation*
Severity Rating	*Very High*	Increase more than 8%	Delay more than 10%	Fatality and/or Permanent Disability	More than 7% reduction in operability performance	Major Spill (Full Response)	Worldwide negative news coverage (Governmental Obstruction)
	High	Increase between 4% to 8%	Delay between 5% to 10%	Major Injury (LTI's)	Between 3% to 7% reduction in operability performance	Serious Spill (Significant Response)	Negative local news coverage (Permitting Delays)
	Medium	Increase between 1% to 4%	Delay between 1% to 5%	Medical Treatment (Recordables)	Between 0.5% to 3% reduction in operability performance	Moderate Spill (Limited Response)	Negative exposure at facility (Emotional Unrest)
	Low	Increase less than $<1\%$	Delay less than $<1\%$	No or Minor Injury (First Aid)	Less than 0.5% reduction in operability performance	Minor Spill (No Response)	No concern

Table C. Example severity quantification.

Endnotes

1. Where performance targets are taken as predictability of Capital Cost, predictability of Project Schedule and level of facility operability after startup.
2. AACE-I Recommended Practice No. 18R-97 (2005) Cost Estimate Classification System – As Applied in Engineering, Procurement, and Construction for the Process Industries.
3. The "Project Readiness Index" is provided by Asset Performance Networks as part of the "Project Pyramid", web-based self-assessment tool for measuring project readiness and project team alignment. See http://www.project-pyramid.com/index.html for further details.
4. Internal Asset Performance Networks database.
5. Steven Edwards, Stephen Williamson, Jacquie Glass, Michel Anderson and Penny Koppinger; "Where There's Smoke… – Achieving Safe and Reliable Operations with Enterprise Risk Management", IBM Global Business Services, July 2008.
6. The guideline can be downloaded here: http://www.ich.org/cache/compo/363-272-1.html.
7. This is a link to the ICH Web site: http://www.ich.org/cache/compo/276-254-1.html.
8. Refer to Annex II of ICH Q9 for examples.
9. Kerzner, Project Management, A Systems Approach to Planning, Scheduling, and Controlling, 8th ed., 2003, Chapter 17.1.
10. Note that this database covers a wide range of process industries. It does not focus exclusively on pharmaceutical projects.
11. Some of these risks, (specifically, those related to oil & gas projects) were discussed in Schroeder, Brett & Jansen, Jan A., "Why Traditional Risk Management Fails in the Oil and Gas Sector: Empirical Front-Line Evidence and Effective Solutions," 2007 AACE International Transactions, RISK.01, AACE International, Morgantown, WV, 2007. The risks related specifically to other process industries than pharmaceuticals have been omitted from this list.

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This article presents four case studies illustrating a wide range of applications for risk-based approaches in pharmaceutical engineering projects.

Risk-MaPP, ICH Q9, ASTM 2500 in Action: Project Advantages of Practical Quality Risk Management Approaches

by Brian Andreasen, Jürgen Blasi, Holger Fabritz, Henrik Feldthusen, Niels Guldager, and Gert Moelgaard

Introduction

For many pharmaceutical companies, the science- and risk-based approach is still new and not straightforward to implement. Although it is at the core of the FDA cGMP for the 21th Century initiative as well as the joint USA/Europe/Japan effort of ICH Q8, Q9, and Q10, many companies are struggling with how to get the principles to work in practice. Several recent guides support the risk management practices, such as ISPE's new Risk-MaPP Baseline Guide,[1] ICH's Q9 on Quality Risk Management,[2] ISPE's GAMP 5[3] the still under development ISPE Baseline® Guide: Science and Risk-based Approach for the Delivery of Facilities, Systems, and Equipment,[4] and PDAs technical report no. 44 Quality Risk Management for Aseptic Products[5] just to mention some.

Rightly applied, the project advantages of using risk management principles really support some clear business advantages. Experience from a number of projects indicate that once the pharmaceutical company's users understand the concepts and start working in cross-technical and cross-organizational teams together with risk-management experts, the learning curve is not difficult to climb.

In May 2007, the ASTM E2500 "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment" was approved.[6] It is a streamlined science- and risk-based approach to ensure "fitness for use" of a manufacturing system in a significantly more cost-effective way than the traditional approach. The streamlining can be done together with an effort to re-think past practices into a new and lean approach that puts the main focus on the critical aspects of the manufacturing system and may enable significant business savings in comparison with the traditional C&Q approach.

To illustrate the applications, benefits, and challenges, four recent case studies are selected from real life projects. They all had a clear benefit from taking the new science- and risk-based approach rather than just following a traditional and much more paper-intensive and costly approach.

1: Risk-Based Approach for Streamlined and Compliant Batch Documentation of a Biotech Process

Introduction

A biopharmaceutical manufacturer wanted to streamline an overly complicated batch documentation system by re-evaluating the requirements and needs with a practical risk management approach based on ICH Q9. The approach should introduce a new batch documentation standard for the biopharmaceutical manufacturer.

The Problem

The main issues were the following:

- Large amounts of paper are produced per batch, which leads to a high verification effort.
- Too much recorded data of no interest, while other relevant data was missing. The recorded data followed no consistent structure throughout the processes, so the batch documentation from different departments was very different.
- Compliance with the 21 CFR 11[7] require-

ments was not implemented in a systematic way.
- Paper-based documentation was mixed with electronic documentation in a compound of batch recordings.

Project Challenge

The challenge for the project team was to establish a method to separate important information from unimportant, identify missing data to close the compliance gaps, and standardize batch documentation procedures across departments.

By applying a holistic risk-based quality approach across all areas, the team succeeded in the complex task and achieved a clear and quality-focused solution out of the large amount of available information - *Figure 1*.

Practice in Project

The risk-based approach was practically applied through Failure Mode, Effects, and Criticality Analysis (FMECA) with the aim to identify and evaluate all quality relevant parameters in the production process and to provide the foundation for the creation of a new uniform, minimized, and GMP compliant batch documentation to get rid of the obstacles mentioned above.

Furthermore, each process step is linked by the FMECA with the previously defined Critical Quality Attributes of the whole process chain.

Because the given process was split up into 22 process steps with many operation steps each, the uniformity of batch recording was achieved through FMECA analysis of risks, parameters, and measurements in a standardized way. Thus standard process steps such as sampling, material input, calibration, data input, cleaning, etc., was described by text modules. It was ensured that comparable risks in comparable operations would lead to comparable documentation measures.

After performance of the FMECAs for each process step, a concept for modular batch recording documents was developed in team work with the responsible persons from Production and Quality Assurance.

During development of the concept, it was found that uniform and GMP compliant documentation of critical operations needs uniform sub elements for, e.g., the set of parameter tolerances, the identification of incoming and outgoing material, the identification of resources as personnel, equipment, etc., the status of equipment concerning calibration, cleaning

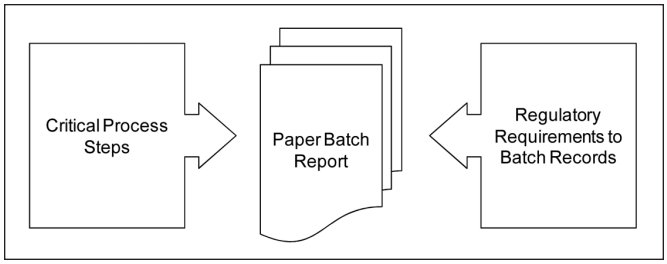

Figure 1. Combination of process and regulatory requirements.

or sterilization. Finally, formal elements, such as document format, approval status, and signature rules were streamlined according to the risk-based rationale - *Figure 2*.

Key Learnings

There were a number of important learnings during the project's duration of several months:

- First, very clear process knowledge is needed not only from the manufacturing and technology point of view, but also regarding the organizational conditions in the facility.
- Second, the risk-based approach to meet product quality is not yet common knowledge in all pharmaceutical companies and it seems to be an unknown tool for the task of batch recording development or other areas of quality management. Risk analyses are more common in terms of validation. This leads to the task that the method should be very well communicated both with the management as well as with the operational units, in order to obtain a substantial quality of the initial risk assessment as well as of the new batch recording concept. Each person involved should have a profound understanding of why it is done.
- Third, there is also a demand for harmonizing coordination between the company's general regulatory approach and the day-to-day approach of the operator.

Conclusion

By application of FMECA Risk Assessment for creating new batch documentation, a significant degree of standardization was realized and a clear, regulatory compliant foundation was established.

Standardization of recording forms allows fast creation of new batch documents for new processes and support the change control procedure. The planned transfer of the current

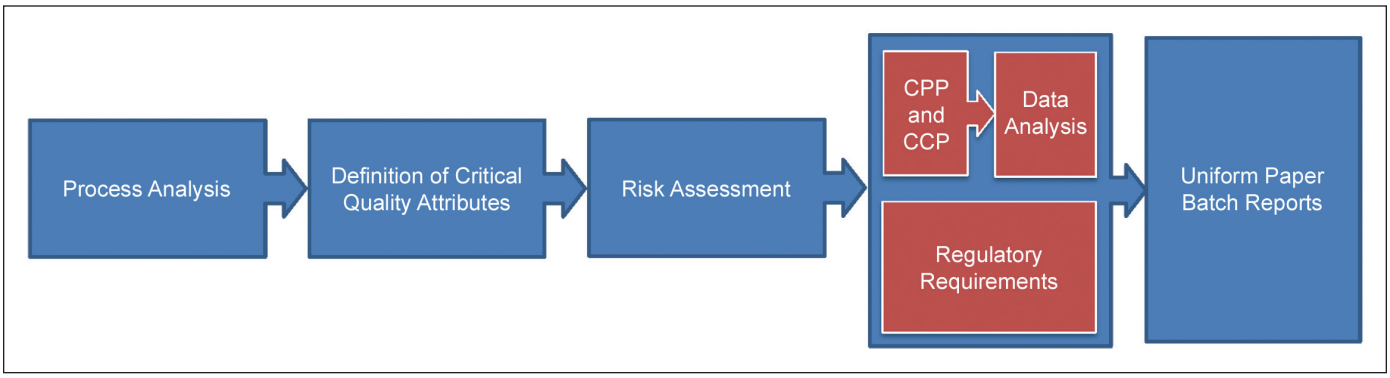

Figure 2. Steps of development of risk-based batch recording system.

paper documentation to a fully electronic system is facilitated as well, because this automation task needs clear structuring of batch record contents.

The outlined methodology focuses clearly on critical quality attributes and enables the customer to reduce the verification effort to a minimum. It is estimated that the time for creating the documents, the batch recording, the verification, and approval of reports are reduced by 20 to 40% with respect to number of required entries.

To achieve acceptance of the risk-based thinking in quality management, it is crucial to have a general buy-in by the management of the company.

2: Verification by the ASTM E2500 Approach in a New Biotech API Facility

Introduction

The involvement in this project began with the first feasibility studies until the facility was in operation, thus covering all planning, engineering, design, construction management, and verification.

The challenge of this project was to implement a new verification approach in a project involving hundreds of people, all coming from a well established and functioning C&Q system. In fact the decision to follow the ASTM E2500 approach was taken very late in the project and this provided some interesting challenges.

Challenges

The decision to follow the ASTM E2500 approach was made very late in the project (after basic design). In fact, all early planning was based on the traditional C&Q approach.

- No project procedures, templates, etc., were defined for the new approach.
- The client's Quality System did not support the ASTM E2500 approach.
- The crucial decision about changing from C&Q to ASTM Verification in this large project was made after investigating the ASTM E2500 approach on a virtual product and during several workshops.
- The results were so promising that the pharmaceutical company and the project management decided that the project would benefit from the new approach even at a fairly late stage. Fortunately, there was time to change to the new verification paradigm.
- It was expected that there would be resistance from the project group (users, QA, and the engineers) and especially nervousness for change to ASTM E2500. All document types, project procedures, activities, routines etc. were subject to major changes that were only briefly defined.
- A detailed roll-out plan for the ASTM E2500 approach was established and adapted to fit into the project's milestone plan.

In headlines, the plan consisted of:

- Initiation of a risk assessment process.
- Establishing a first, illustrative ASTM E2500 verification example approved by all interests in project in consensus, including an independent and internationally recognized cGMP specialist.
- Roll-out, i.e., start training, develop new project procedures, create deviations to existing quality system, update the project task plan, etc.

The Risk Assessments

Training of the project team in the risk management methods was done as a workshop with people from the manufacturer's main areas, including development, pilot, process, operation, maintenance, and QA together with lead engineers from NNE Pharmaplan.

The risk assessment of the process and equipment was executed based on evaluating the Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs). Fortunately, the CQA and CPP for the biologic API were very well defined, challenged, and documented from the pilot plant team and the workshops were conducted as cross-organizational and cross-disciplinary workshops that proved highly productive.

Because of the process development knowledge supplied by the pilot plant team, it was easy for the entire panel to discuss and define an engineering control strategy to mitigate the risk of deviations in critical process parameters and to detect and manage such devitations should they occur.

The Illustrative Example

A complete "Quality Package" (design, review, FAT, SAT, IQ, OQ, PQ) of an Ultra Filtration module from a similar project was used as an example and transformed to the ASTM E2500 Verification approach inclusive of non-conformities, change management examples, etc.

After the workshop, the new risk assessment with consensus about the risk in real life (taken from the "well known and real world"), was fairly easy for the group to develop the new verification approach package. All people could relate to the equipment and they could remember the problems, the tests, the non conformities, etc.

The Broad Project Roll-Out

Having the two comparable examples with reference from "the real world," it was very visible to demonstrate the differences between the old and the new approach to the entire project group – and the benefits of a change were clear: The ASTM E2500 approach resulted in approximately 50% reduction of all quality related documentation.

The launch of the illustrative example was the turning point for the feelings about the ASTM E2500 standard in the project. Everybody could see how they fit into the concept, the way they should take responsibility, and how they should contribute to the verification approach. The common mood for the changes was very positive from that moment. Most importantly, QA could see the light. Because of the stringent and transparent hierarchy of documents, where the critical aspects were systematic broken down to design issues and mitigated down to the least extent possible, it was easy for

QA to extract what was critical to the product and patient safety and where they should put in their effort.

The Verification Activities

The critical aspects, including the derived engineering control strategy which mitigate the risk for occurrence and ensure detection, were copied to verification plans and broken down to acceptance criteria for the verification activities. All test activities were generally performed by the vendors during FAT and SAT, including tests for the critical aspects.

It was agreed with vendors that they also should test for correct implementation of the critical aspects according to methods and test procedures provided by the project. In this way the project could ensure and manage that all the critical aspects were appropriately challenged and tested for correct implementation.

In traditional C&Q projects, the Subject Matter Experts (SMEs) were mostly involved during the FAT/SAT activities, but with the ASTM E2500 approach, their responsibilities were clearly broader. The SME's realized that they should test and inspect to find errors early, because there would be no second attempt during IQ/OQ. One has to ensure correct implementation and challenge of the equipment in the first shot.

The Bottom Line

Despite some effort to implement the ASTM E2500 approach, the execution of a set of risk assessments, creation of a common culture, etc., led to overall savings of an estimated 50% compared to the originally planned, traditional, C&Q approach. Furthermore avoiding the many trivial and often repetitive tasks from planning and qualification in the traditional C&Q approach gave a much more result-oriented project culture with a willingness to get it "right first time."

The savings were not the only reason for the pharmaceutical company to change to the new ASTM E2500 approach. Other key drivers included the benefit of a more robust process, transparent document structure, and SME involvement and responsibility for quality. Furthermore, the company also wanted to be proactive to meet future compliance issues.

Key Learnings

Change management – it is possible to change to a new approach and create a positive common culture for the ASTM E2500 approach even if you come from a very well respected, traditional system.

In this case, the project started behind schedule because of the last minute decision to use the new approach, but the team was united and the benefits convincing. Change management was the key to success, as well as the buy-in from all parties involved.

Risk assessment should be executed at the right time. Several mitigations for product and patient risk were identified during the risk assessment and design review sessions.

The suggestions often impacted the project scope and design of the equipment, so it was not always possible to implement the suggestion to the design in that late stage of the project.

Thus some mitigation had to be implemented in SOPs and controlled manually. This situation was frustrating for the people performing the risk assessment. If the new knowledge gained during the risk assessment were introduced three months before, the implementation would have been possible with no impact on cost or time schedule, resulting in a more robust and safe process.

Risk assessment is ideal for technology transfer and for new ideas to ensure a robust and safe process. However, the most crucial learning and recommendation for the future is to start the risk assessment in due time. It should not be a "desk exercise" after the design is decided. By taking the initial cost for the risk assessment before one freezes the scope and by using it actively during the design process is the best way to put risk management to work.

3: ASTM E2500 Verification Approach Applied for the Design, Construction, and Verification of a Greenfield Biologics Pilot Plant Facility

Introduction

This case is about an ongoing Engineering, Procurement, Construction Management, and Verification (EPCMV) pilot facility project based on risk- and science-based verification principles according to the ASTM E2500 as well as the ICH guidances Q8, Q9, and Q10. The project includes activities from detailed design through construction to verification (formally known as Commissioning and Qualification). Final handover is planned for June 2012.

Challenges

- Multiple process facility (pilot plant).
- Requirement specifications and potential risks not initially aligned, as risk assessments on equipment level were not included in the front end study (basic design).
- Time pressure with respect to the preparation of risk assessments and initial tenders for long lead items, as changes to the design after contract closure will inherently lead to change orders.
- R&D knowledge not captured in the requirement specifications prepared during the front end study (R&D Subject Matter Experts not consulted).

Aim

The aim of the project is successful implementation of a verification strategy, clearly defined Good Engineering Practices, and to catch up with the risk assessment delay in order of priority.

Practice in Project

As no product specific process can be defined for a pilot facility, a template process has been developed with input from existing commercial products. The template process has been used by R&D to delineate Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) inspired by the methodologies described in the recent A-Mab case study set out by the CMC-Biotech Working Group.[8]

Subsequently, when new products are introduced, a gap analysis must be undertaken against the original template process and quality risk management plan, to determine and document any additional controls or measures required to assure the quality of the CQA.

The CQAs and CPPs derived for the template process were used as input to the equipment specific risk assessments and each process step was investigated for potential failure modes. Based on the process flow diagram of the facility the upstream- and downstream processes and supporting systems were divided into 11 main workshops with the purpose of identifying equipment specific critical aspects to go into the verification control strategy.

The project is ongoing and after finalizing the risk assessments, the effort at the time of this article, is focusing on streamlining and revision of procedures for Good Documentation and Testing Practice, Good Engineering Practice, design review, vendor assessment, and SME appointment. Although readily at hand from traditional C&Q projects, it seems that these procedures are cumbersome, outdated, and highly related to a cGMP production environment with too little focus on what is actually required by Good Engineering Practices.

The projected savings on quality related documentation are approximately 50% compared to the traditional C&Q approach and the projected reduction in Quality function manpower to support the project is in the range 50 to70%.

Key Learnings

The best time to decide on applying the ASTM E2500 Verification principles is in the beginning of the basic design phase so that the outcome of risk assessments can be incorporated into requirement specifications.

Equipment risk assessments of the core process with input from R&D, QA, maintenance, and process SME's are highly important with respect to knowledge transfer.

However, not all risk assessments require input for R&D. Risk assessments for process support can be initially carried out by the EPCMV integrator and subsequently reviewed and approved by QA and process SMEs.

A very clear understanding of critical aspects, Good Engineering Practices, and general assumptions of a normal cGMP production setup is important, in order to limit the verification effort of failure modes derived from each of the process steps.

Critical issues such as sanitary design, operator training, loop testing, calibration, and routine maintenance are important and must be addressed by SMEs during project execution. However, these issues are captured solely by GEP and the cGMP production setup and should not be included in the final and QA approved System Acceptance and Release Report.

Conclusion

The application of the ASTM E2500 verification approach may seem difficult to handle at first; however, the tools and principles of risk assessments and verification of vendor prepared tests are not new and not difficult to implement.

As a result of the verification methodology, duplication of tests are avoided and focus is intensified to the areas with the highest risk to patient safety. Furthermore, flexibility in project execution is increased and the Total Investment Cost reduced to the benefit of the overall quality going into the project.

4: Product and Process Risk Assessment as Framework for Robust and Effective Development of User Requirement Specifications in a Biotech Facility Project

Introduction

The User Requirement Specification (URS) was traditionally a core document for the traditional way of executing a biotech facility project. In this case, the company wanted to keep the URS-based concept; however, with an adaptation to a practically applied product quality risk management approach.

Challenge

Biotech equipment can be complex, expensive, and often customized to fit the intended processes. Thus setting up requirements for biotech equipment can be time consuming. Furthermore, there is a tradition in many companies for design-requirements that are not directly product quality related, partly because of a tradition to keep all requirements in one document. These factors can lead the qualification effort becoming larger than needed than seen from a strict product and process quality viewpoint.

Aim

Typically, the process/product subject matter expert team also has qualifications on safety-, financial-, and standard practice issues so the aim was to capture this expertise to accelerate and structure the specification effort.

Clearly some requirements would not be directly product related, but still very important typically for safety reasons or for the shear amount of investment involved in the equipment, so they would need to be documented, but should not enter the quality assurance approval work cycle.

A shared understanding of product critical requirements slated for qualification and quality assurance approval and other design requirements needing only commissioning approval was deemed essential for a fast and effective project.

Previous project experience had shown that lack of clarity in product significance of requirements could lead to overwhelming qualification work and the quality assurance function becoming a bottleneck in later project stages, especially in inevitable deviations from requirements stated years before the equipment was qualified.

Practice in Project

A documentation format for initial process risk assessments was developed, in which a given process step could be evaluated in a structured manner for impact on product/process, safety, financial, or standard practise issues.

Subject Matter Experts from Development, Manufacturing, Maintenance, and Quality Assurance were gathered for the

1 Process Risk Assessment

Product Quality	Yield	HSE	Design
Membrane pressure difference	-	Noise acceptance level	Possibility to use both hollow fiber and cassette systems
Cleaning and sterilisation of all product contacting surfaces	-	-	Possibility for aseptic sampling in surge and hold tank
Temperature in Surge and hold tank	-	-	-
Flow over membrane	-	-	-
pH in hold tank	-	-	-

2 User Requirement Specification

Req. No.	Req. Class: (C/Q)	Description	Process Range	Target Uncertainty
1	C	It must be possible to change the microfiltration part of the unit from hollow fiber modules to cassette systems.	N/A	N/A
2	**Q**	A sample port must be installed in both surge tank and permeate tank. Sample port to be placed as close to the bottom as possible.	N/A	N/A

3 Requirement Classification

Req. No	C/Q	Description	Disturbance Potential disturbance on non-performance of requirements	Consequence Potential qualitative consequence of disturbance	Preventive Measure Current preventive measure against potential consequence
		4 Process Requirements			
1	C	It must be possible to change the microfiltration part of the unit between hollow fiber modules and cassette systems.	Change not possible	No consequence for product quality, for production flexibility	N/A
2	**Q**	A sample port must be installed in both surge tank and the permeate tank. Sample ports to be placed as close to bottom as possible.	Aseptic sampling not possible	**Sampling can be critical for determination of product quality**	None

Figure 3. Documentation examples excerpts for microfiltration unit: the novel process risk assessment approach filtering out design and quality requirements, 1. the resulting requirement statements in the URS, 2. the requirement classification, 3. providing the rationale for product criticality of requirements (c: commissioning, q: qualification). Note: sample valve detail being moved up from design issue to product related requirement.

process risk assessment work sessions that took place over one full day for the process from the vial back to the processed bulk. The process risk assessment format acted as "conversation starter" and facilitated structured drafting of requirements and the rationale for these requirements. The completed process risk tables where then used as basis for developing user requirements with requirements marked with Qualification or Commisionning depending on impact on product quality or not. Draft user requirements were forwarded for final editing and approval. Rationales were collected into a requirement classification document providing the overall rationale for selecting or de-selecting requirements for qualification.

Key Learnings

The process risk assessment approach provided an inclusive platform that clearly allowed the project group to develop a shared vision of the roadmap to effectively qualified and commisioned equipment. As this hybrid approach did not reduce the number of documents involved in the process in Figure 3, there was no reduction in documentation or workload. The advantage was on qualitative in setting the right perspective from the start

Accordingly, the largest success factor was the abiility to gather all shareholders together for the process risk assessment session. Although the group of subject matter experts and the process risk assessment format would provide a good basis for qualified and directed discussions, we found that the appointed facilitator to drive the process also had a relevant role. Kick starting the effort with a one-day session allowed parallel development of all documents thus shortening timelines for finalization since all shareholders were involved from day one. In a project setting, this approach also allowed fast establishment of channels of communications so that approval of requirements also could be obtained very fast.

In conclusion, it can be said that the requirement specification must be treated with respect as rather complex requirements must be stated in relatively few words – and the requirements are verified a good period of time after they were stated. It is clear that written statements can only do so much in ensuring that process equipment lives up to all requirements.

The importance of close supervision and follow up on equipment design, manufacture, installation, and testing can not be underestimated – but an upfront structured approach can provide the framework for timely and sufficient focusing on key requirements.

Conclusion

As initially stated, many pharmaceutical companies still find the science- and risk-based approach new and not straightforward to put in action.

These four case studies of risk-based approaches applied to different aspects in pharmaceutical engineering projects and tasks were examples of useful de-mystifications. They illustrate the wide range of possibilities and applications for risk-based approaches in pharmaceutical engineering.

Experience from these case studies and other projects shows that rightly applied, the Quality Risk Based concepts combined with solid Product and Process understanding and Good Engineering Practices, really helps toward cost-effective and streamlined approaches with clear customer benefits if applied right. If not applied right, they simply add a new layer of paper to the traditional practices, without adding any benefit and with the risk of sacrificing true product, process, and project knowledge.

In short, if you don't know how to identify what's critical, you won't get the benefit, but just another pile of "dead wood" of risk assessment papers. Which should be in nobody's interest.

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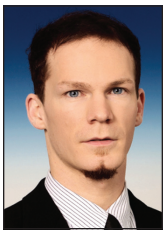

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A Quantitative Study in Cross Contamination

by Julian Wilkins

This article is based on data acquired during an evaluation of the quantifiable risk of cross contamination in an Oral Solid Dosage (OSD) facility. This article is intended to provide some quantitative data to an area in which perception and not reality is the norm. There is really no published data on cross contamination.

In 2005, it was clear that regulators around the world were considering adopting segregation and dedication for all "compounds of concern," such as genotoxic, mutagenic, carcinogenic, hormones, sensitizers, and beta lactams. The impact to industry would be incalculable. The reason for this move was the perception that cross contamination was rampant.

Setting Limits

The perception is that there should be no cross contamination of one product by another, but how do you define "none." Some regulators have used zero as the limit, but it is impossible to demonstrate zero. Another method has been "below the level of current detection methods." In the past two decades, the limit of detection for Naproxen Sodium has fallen from about 4 nanograms to 250 picograms. Looking at the data collected in this experiment if such a standard were applied, **all** pharmaceuticals should be produced in a segregated and dedicated way, including any handling of drug substance in the pharmacy or by caregivers. As will be discussed later, cross contamination of a single dosage is a greater risk than cross contamination of bulk API/excipients prior to final blending/mixing or other processes that ensure uniform distribution.

There are various ways limits can be set for pharmaceutical compounds. By far the most scientific is one based on toxicological data setting a health-based limit, such as an Acceptable Daily Exposure (ADE). An ADE is a daily dose of a substance below which no adverse effects are expected by any route, even if exposure occurs for a lifetime. The same data is used to calculate Occupational Exposure Limits (OELs). The major difference in the two terms is that the OEL is used to protect the operator/worker whereas the ADE is used to protect the patient.

Design of Experiment

In this particular case, the owner wanted to understand how effective their development scale OSD facility was for both operator protection and cross contamination. To determine if cross contamination was occurring, air sampling, product contact, and non-product contact surface swabs where taken as well as the surrogate/placebo sample test. These samples were used to see if they gave clues as to how cross contamination might occur, using data rather than perception. For occupational exposure, area and personnel sampling was used for iteration 1. The personnel sampling was omitted for iterations 2 and 3 as described below. To robustly understand if cross contamination was occurring, sequenced production of surrogate and placebo tablets was performed.

The Procedure

Basically the procedure was to run a surrogate material through the oral solid dosage process including end of run cleaning and then follow up with a placebo material run through the same processes, and with three iterations of the surrogate/placebo cycle. For each run, area air samples and swabs were taken with placebo tablets pulled for testing at the start, middle, end of compression, and after coating. 100 tablets were taken at the stated points, bagged separately, and labeled. They were sent to a certified independent testing laboratory for analysis. The laboratory selected three tablets at random for sampling from each placebo batch and each sampling point (start, middle, end, and coating for each of three iterations). Tablets with Naproxen Sodium as the active were made for each of the three surrogate batches. Table A shows the sequence of surrogate and placebo as well as the dose per tablet and total dosages manufactured in the batch.

Production Sequence	Amount	
Surrogate 1 (S1)	300,000	300 mg Naproxen Sodium
Placebo 1 (P1)	300,000	300 mg placebo
Surrogate 2 (S2)	300,000	300 mg Naproxen Sodium
Placebo 2 (P2)	300,000	300 mg placebo
Surrogate 3 (S3)	300,000	300 mg Naproxen Sodium
Placebo 3 (P3)	300,000	300 mg placebo

Table A. Production sequence.

Surrogate Run 1

As part of a surrogate test protocol, artificial events are not induced to represent worst case scenarios. Our experience shows that real world events regularly occur in surrogate runs because the operators are unfamiliar with the equipment. So surrogate run 1 demonstrates how real world conditions can occur without any artificial stimulus. The full Industrial Hygiene (IH) protocol sampling was to occur for each surrogate iteration. Due to the amount of time taken and the incidents described below, it was decided to dispense with IH sampling for surrogate runs 2 and 3.

What Occurred

The system was new and had undergone IQ, OQ, and PQ. The staff was not very familiar with the equipment and its operation which during a surrogate run is preferable to mimic real world conditions.

- Material was weighed in an isolator and passed into a bin connected by a split butterfly valve. In designing the system, no provision had been made for misalignment or support of the bin when docked. As a result, the bin was placed by the bin handler as accurately as possible.
- Once docked, the bin handler was removed to allow the operator access to the isolator.
- The active was added to the bin from the isolator. At this point, the bin and contents were hung off the base pan of the isolator at a weight of about 150 kg after dispensing into the bin.
- The bin handler was placed and an attempt to disconnect the Split Butterfly Valve (SBV) was made. Eventually a rubber hammer was used. When the valve finally parted, the isolator base sprang up by 1 1/2" or so shaking both parts of the SBV to open and allowing product to escape. The energy produced caused visible powder clouds.

As part of the fluid bed processing function, a compressed air pulse is used to clear the sock filter. This pulse is injected on the exhaust side of the filter sock and is meant to dislodge product into the product bowl. As configured, a gasket had not been cut to profile on a relief vent. As a result, the pressure pulse had no where to go (the exhaust valve is closed during purge) and the relief valve actuated allowing the over pressure to be relieved. As designed, the fluid bed processor relieved into the technical space, designed to withstand relief and control its efflux to atmosphere via the exhaust HEPA filters. The technical space has its own HEPA in/out filtration and has Material Air Locks (MALs) and personnel air locks (PALs) to contain the space from the external cGMP corridor and the environment.

In addition, a pulse purge on the vacuum transfer caused visible and measurable emission. This occurred because the quick connects on the vacuum transfer were not identified due to incorrect installation. As a result, the pressure pulse was not vented and found every weak spot in the system (notably no gasket was present on the spray granulation plate of the fluid bed processor) and a visible powder plume resulted.

A technician rectified the items above before surrogate run 2 and the problem did not recur. However, to be monitoring the equivalent of an explosion venting of a fluid bed processor was a unique experience and provides some very valuable data.

The design for off loading the fluid bed processor was:

- vacuum discharge to bin
- bin docks to mill
- mill discharges to bag
- bag is placed in the isolator
- isolator discharges to blending bin

Because significant exposure occurred in surrogate run 1, it was decided to discontinue IH data collection. However, area sampling in all the rooms in which the operations occurred, the in suite corridor, the GMP corridor, and the technical space continued to be monitored for each iteration. This was done so that airborne concentration based on emission could be compared with the placebo tablets to see if there was any correlation between air concentration and cross contamination.

The Data

The main purpose of the experiment was to show how much of the surrogate was present in the three placebo runs, regard-

	Placebo Tablets (mcg/tablet)		
	1P	2P	3P
S1	0.019	0.025	0.170
S2	0.025	0.029	0.160
S3	0.020	0.023	0.210
M1	0.019	0.024	0.200
M2	0.021	0.024	0.170
M3	0.018	0.021	0.340
E1	0.019	0.026	0.190
E2	0.025	0.025	0.180
E3	0.018	0.031	1.300
C1	0.034	0.020	0.170
C2	0.019	0.031	0.160
C3	0.021	0.023	0.200
S = start, M= Middle, E= End, C= after coating P= Placebo Run			

Table B. Results of placebo test.

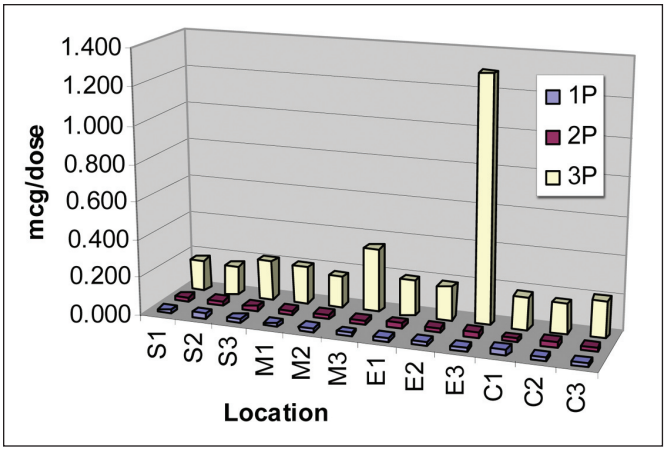

Figure 1. Placebo results.

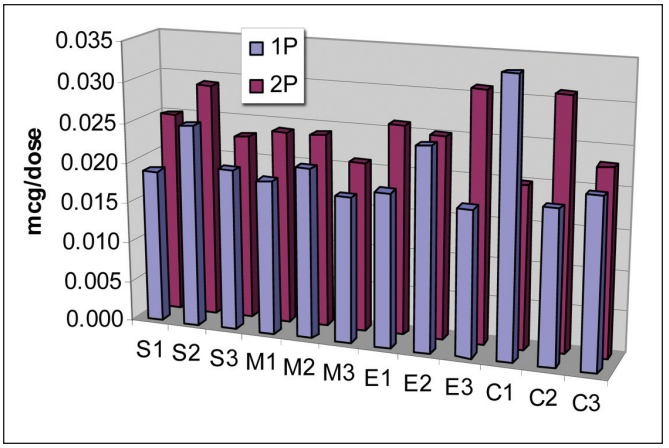

Figure 2. Placebo results for Iterations 1 and 2.

less of the route of exposure. A test like this is holistic as it includes all routes of exposure.

Table B shows the concentration in micrograms of Naproxen Sodium in the placebo tablets for each of the three runs.

Results of Placebo Testing

From 100 tablets collected at the each of the stages (beginning, middle, and end of the compression stage and after coating), three samples were randomly collected from each sampling stage for analysis at an internationally recognized laboratory with a well developed method for detecting Naproxen Sodium. In Figure 1, Placebo run 3 (P3) shows results that are significantly out of line with Placebo run 1 (P1) and Placebo run 2 (P2). To keep things in perspective, even at the results of Placebo run 3, it would pass the FDA Genotoxic limit of 1.5 mcg/day, although it is very close to the limit.

Figure 2 shows Placebo runs 1 and 2 which show a consistent set of results. Placebo runs 1 and 2 are consistent in the range (0.18 – 0.34 mcg/tablet). Placebo run 3 was significantly worse and had an outlier.

What caused Placebo run 3 to return inconsistent results? It could have been contamination by being in the same shipper as the surrogate tablets. But it is highly unlikely that it would lead to such consistent results, other than the outlier. Additionally, Placebo run 2 was in the same box as Placebo run 3 and was consistent with Placebo run 1 which was sent separately. All samples were in zip lock bags. The laboratory sampled another set of tablets which verified the results consistent with the other samples from Placebo run 3 without an outlier. The most likely explanation is that this is real data and that Placebo 3 was contaminated at a higher level than Placebo runs 1 and 2 at some point and that the outlier could represent a tablet that was additionally contaminated when in single dosage form.

A product is more vulnerable to cross contamination when it is in a single dosage form because the amount of the contaminating compound needs to be below the ADE to keep the risk of cross contamination low because there is no expectation of uniform dispersion once in the dosage form. However, before this stage, the limit would be the number of daily doses present in the batch times the ADE (300,000 daily dose × 1.5 mcg/day = 0.45 grams).

Therefore, final blend transfer, compression, coating, and packaging are the most vulnerable operations for cross contamination and processes prior to blend uniformity are less vulnerable by significant orders of magnitude. This may seem counter intuitive; it is not.

What caused this increase in carry-over?

1. Was it sedimentation from the concentrations created in the process rooms and technical space and tabulated below?
2. Was it mechanical transfer?
3. Was it retention on critical product contact surfaces?

Airborne Concentration

Note the data in Table C is based on long duration samples

Airborne Concentration (mcg/m3/Duration)								
	1S A Form	1S Gran Mill/B	1S Comp	1P	2S	2P	3S	3P
A Granulation	0.1600	0.6900		0.0060	0.6200	0.0180	0.1500	0.0041
B Granulation	0.0920	0.7500		0.0032	0.3300	0.0150	0.1500	0.0013
Compression			0.0023	0.0002	0.0072	0.0016	0.0086	0.0005
Coating			0.0025	0.0003	0.0007	0.0007	0.0051	0.0002
Corridor in Suite	0.0005	0.0400	< 0.0002	0.0002	0.0015	0.0005	0.0043	< 0.0002
Corridor outside	< 0.0002	0.0035	0.0005	0.0005	0.0033	0.0006	0.0004	0.0004
Tech space	28.0000	230.0000	0.0800	14.3000	100.0000	5.0000	41.0000	5.6000

Table C. Airborne concentration results.

of five to nine hours.

1S A Form = Formulation in the first surrogate run where the split butterfly valve exposure event occurred

1S Gran/ Mill B = Granulation, first surrogate run where the fluid bed processor venting occurred

1S Comp = Compression/coating first surrogate run

1P = first placebo run, backgrounds, no personnel samples

2S = second surrogate run, no personnel samples

2P = second placebo run, no personnel samples

3S = third surrogate run, no personnel samples

3P = third placebo run, no personnel samples

Location of Samplers

Granulation – two background samples at different corners of the room

Compression – background during operation of the press
Coating – background during operation of the coater

Corridor in Suite – single door to process room, pressure cascade to the process room

Corridor Outside – cGMP corridor outside the suite protected by airlocks with two chambers

Tech Space – area sample in the technical space during the surrogate and placebo runs

Layout of Facility

The data are very low in the process rooms despite two visible dust cloud events. The technical space is a different story, but there is no route for this material to return to the placebo and by iteration 3, the results even in the technical space are far lower than iteration 1 - *Figure 3*. The conclusion is that airborne

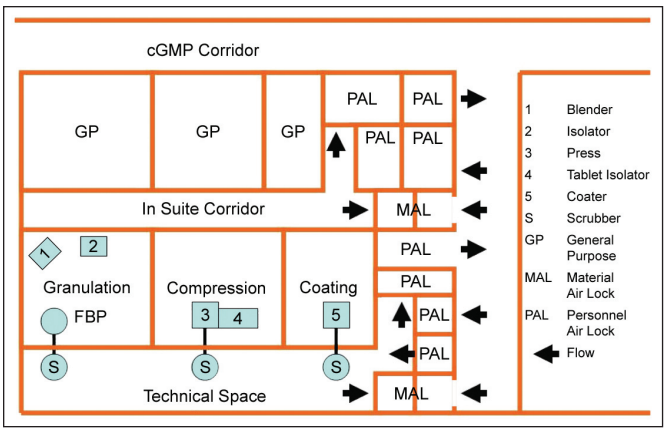

Figure 3. Layout of facility.

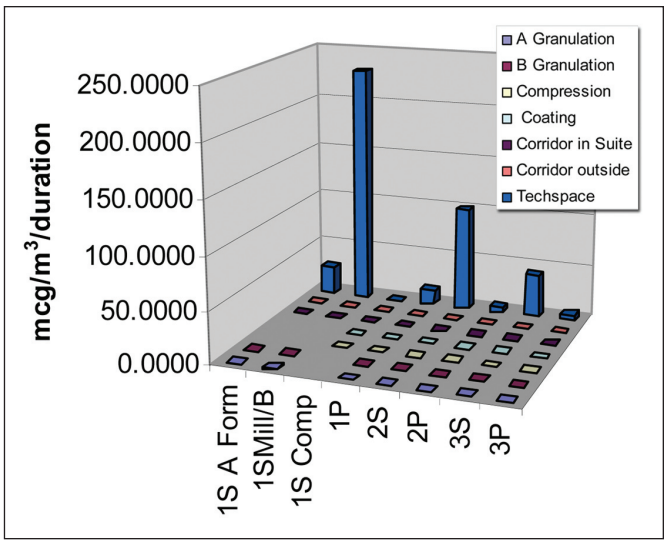

Figure 4. Air concentrations all spaces sampled.

concentration does not affect the carryover in this case.

Air Concentrations all Spaces Sampled

Figure 4 includes the technical space results which graphically overpower the much lower non-technical space results shown below. The technical space airborne concentrations are of interest because the fluid bed processor, press, and coater all used scrubbers to collect the dust. Scrubbers are very poor dust collectors (as can be seen by the results). In addition, the fluid bed processor vented to the technical space in iteration 1.

The technical space is negative in pressure to the other areas and is protected by MAL and PAL and is vented to the outside via HEPA Filters. It is constructed like the manufacturing rooms. When the result of the other areas are compared to the results in the technical space the data becomes insignificant. The technical space figures are very high for the Fluid Bed Processor (FBP) venting, but drop to lower levels during compression, so the room air handling dealt with clearing out the concentration. The figures dropped iteration to iteration. The concentrations in the technical space make it clear that the wet scrubbing is not efficient at removing particulate. The press and coater scrubbers are much more effective or have considerably less load than the FBP scrubber.

Air Concentrations except for Technical Space

Figure 5 represents the concentration without the technical space figures. Granulation continued to be significantly higher than other results even though the results got better. This may be an improvement in technique, but is more likely caused by the pulse purge "finding" weak spots in the fluid bed processor connections.

The non technical space concentrations are interesting because:

1. The in suite corridor with single door to the process rooms performed very well.

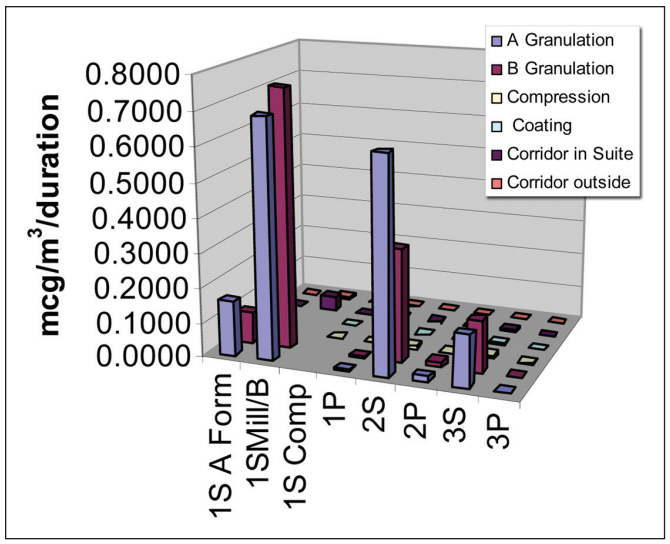

Figure 5. Air concentrations except for Technical Space.

2. The air handling system effectively cleaned up the airborne concentrations between the iterations
3. The concentrations in the granulation room fell with each iteration and were very low during placebo operations showing excellent clean up by the air handlers.
4. The in suite corridor and external corridor were inconsistent; the external corridor had unexpectedly high concentrations when compared with the in suite corridor.

The granulation process caused room concentrations, but as the iterations proceeded and the staff got more familiar with the process the concentration reduced. The issues with the granulation process led to a higher reading in the common corridor, but these results are much lower than would be expected for an open process. The figures would be acceptable for a compound with an OEL of 1 mcg/m^3/8 hours.

Air Concentrations in the Corridors

Other than the issues with the surrogate 1 run (1S), the in-suite corridor performed extremely well, in fact at times better than the corridor outside the suite - *Figure 6*. This defies logic, but a possible explanation is the concentration in the technical space migrated through the building structure to the corridor.

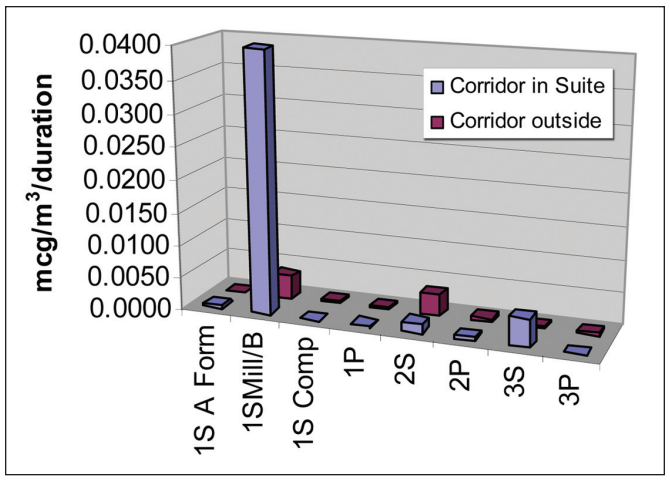

Figure 6. Air concentrations in the corridors.

The final analysis is the swabs; the area of interest is the Product Contact (PC) surface values. However, the tablet samples were collected in the tablet isolator and it is highly probable that contamination occurred here for the outlier - *Table D*. If this is the case, more work needs to be done to understand what caused the contamination. One hypothesis is that material residual in the isolator and on the gloves was mechanically transferred to a tablet during collection. With only one data point there is too little evidence that this was the case, but it is the most likely option since the press product contact swabs provided excellent results. More work is required, but it is possible that three classifications of contact surfaces are required. For example:

Product Contact (PC) – In product contact requiring cleaning to the best possible results comfortably below the hazard-based limit.

Product Near Contact (PNC) – Surfaces such as an isolator wall, floor, and especially gloves. May require cleaning to the standard of product contact surfaces.

Non-Product Contact (NPC) – Surfaces such as floors, walls, and ceilings in processing rooms, etc. A visually clean limit should be sufficient for these surfaces.

This would be in line with the statement that the highest risk of cross contamination occurs once the product is in dosage form.

The figures are unremarkable except for the fluid bed processor and the material and personnel airlocks. The issue of concern is the fluid bed processor, because it has by far the

Swabs	mcg/100 cm^2		
Location	**1P**	**2P**	**3P**
Mill PC	0.150	1.000	
Isolator Floor	1.600	3.300	1.400
FBP Product Contact	16.000	3.300	34.000
FBP Product Contact			53.000
Blender Product Contact	0.140	0.330	
Granulation Floor	14.000	1.300	5.100
Tablet Isolator Non Product Contact	0.130	32.000	3.600
Turret Product Contact	0.028	0.750	
Coater Product Contact	$<$0.010	0.011	0.130
MAL 1 Floor	0.150	3.100	1.100
MAL 2 Floor	0.340	3.300	2.800
PAL 1 Floor	0.340	19.000	
PAL 1 Bench	0.120	0.840	2.600
PAL 1 Floor	2.700		
PAL 2 Floor	0.036	0.320	0.130

Table D. Swab results.

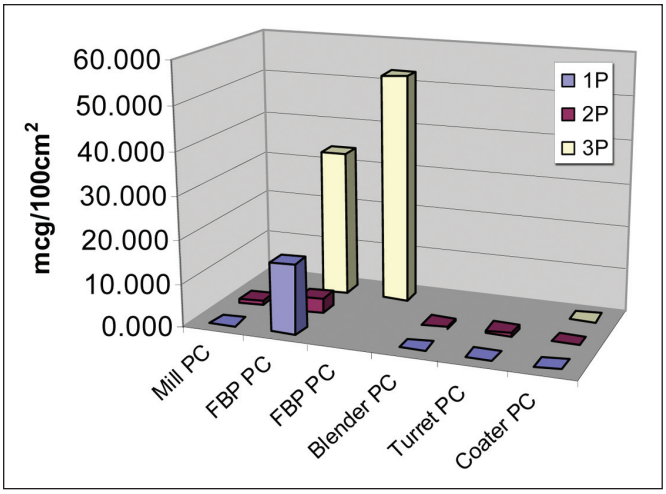

Figure 7. Swab results.

largest surface area. When calculating cleaning limits, the shared surface area is taken into account where the larger the shared surface area as typically found on V blenders and fluid bed processors, the lower the concentration has to be to meet the criteria.

What it does show is a significant increase in concentration in the placebo run 3 coinciding with the increase in the placebo run 3 tablets. All the data was taken post cleaning from the previous surrogate batch. The placebo run 1 should be the worst, using current logic because the airborne concentrations are higher. Placebo run 2 was better, while placebo run 3 was much worse. During the swab recovery, the CIH taking the samples visually identified a contaminated area and took an additional swab. It is clear that the concentration in iteration 3 is far higher than the other runs and undoubtedly is the cause of the increase in concentration in placebo run 3, but due to blending after fluid bed processing is unlikely to cause the outlier - *Figure 7*.

The reasons for this failure and their detection under normal cGMP operation are the key lessons to be learned. In the end, it is all about cleaning. In addition, it does show that airborne sedimentation and mechanical transfer in most cases are a distraction rather than a cause.

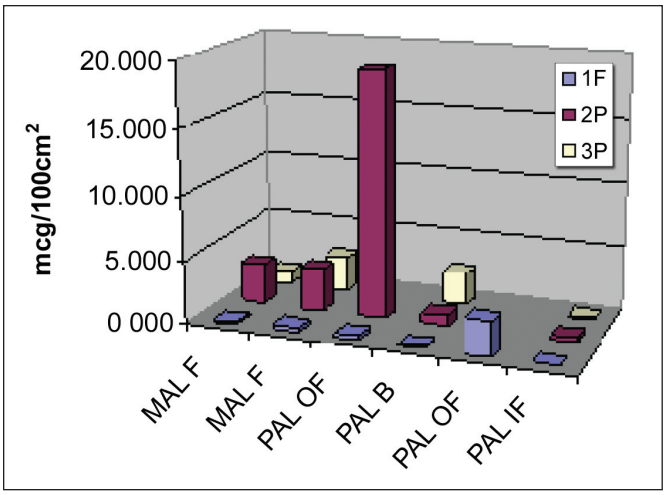

Figure 8. Swab results for each iteration – airlocks.

Note the tablet isolator figures. Tablets were recovered at this point except for coating. Note the results for the coater are getting progressively worse. It is highly probable that the outlier E3 found in Table B in the third placebo run was contaminated by a single (very small particle) as a result of collection in the tablet press isolator, which was contaminated significantly in placebo runs 2 and 3, due to failure to clean effectively and failure to inspect. The isolator had no lighting so identifying visually clean was difficult.

The events in the material and personnel airlocks did not follow the pattern of events in the process rooms and this is indicative of the random nature of results in airlocks. The airlocks tested were double chamber with separate in and out chambers. As a basic rule, expensive and complex airlocks can be defeated by operator technique.

The material airlock data showed that the second iteration had issues. As for the personnel airlocks, the same effect was seen in placebo run 2, while the bench remained relatively clear of contamination - *Figure 8*. Again there is no evidence of carryover from non-product contact swabs except for the tablet press isolator which was used to capture the tablets.

Conclusions and Lessons Learned

1. The test runs as performed represent a true worst case scenario. Are there improvements and controls that can reduce the values seen? Set acceptance limits for cleaning, swab and visual inspection and then monitor performance. Use the hazard-based calculation based on the ADE.

2. The surrogate chosen, the process equipment selected were all worst case. The important factor to consider is the shared surface area to volume processed ratio. The larger the shared surface area ratio the lower the rinse or swab limit will be. The fluid bed processor is significantly the largest shared surface area in this case.

3. Investigation for contamination pathways for fluid bed processor. The supply and exhaust ducts are undoubtedly contaminated, but are not cleanable. Out of sight is not out of mind.

4. Vent fluid bed processor to roof. Discharging to the technical space for explosion relief is not recommended. It is far better to use a 12 bar rated construction with suitable valves.

5. Replace the scrubber with a dust collector for the fluid bed processor and keep the technical space clean.

6. Evaluation on a case by case basis is essential to ensure that anomalies are investigated.

7. Improve MAL and PAL operation, procedures, and wipe down after use. Complex MALs and PALs are not necessarily better or necessary.

8. Split Butterfly Valves should never act as the support for equipment.

9. Compensators for docking inaccuracies are essential.

10. Bins should be on a docking station which allows accurate docking to take place and supports the bin rather than manual alignment.

11. Expect the unexpected.

12. There was no correlation between airborne concentration and cross contamination.

The results show cross contamination occurring at measurable levels. Because it can be measured does not mean it is unacceptable; cross contamination in the worst case was 1.3 mcg/dose. That is 1.3 millionths of a gram. Say the ADE is 10 micrograms, was the risk to the patient unacceptable? The real issue with the results shown is that they were not consistent.

About the Author

Julian Wilkins is Founder and Vice President of PharmaConsult US, Inc. In 1991, he founded a UK based isolator company for the emerging need for pharmaceutical containment. The company carried out many projects worldwide for aseptic and potent containment at all scales of pharmaceutical operation. He moved to the US in 1997 and set up PharmaConsult US in 1999. Since its formation, the company has provided independent advice, design, and support for containment projects, including Bristol-Myers Squibb, Chiron, GSK, Merck & Co., Pfizer, Roche Colorado, Sanofi Sythelabo, Tyco/Mallinckrodt, and Wyeth. Wilkins is a past recipient of the prestigious ISPE Member of the Year award. Wilkins has spoken at many seminars worldwide on the subject of containment and has contributed articles and chapters to periodicals and books on containment. Wilkins has been an active collaborator with ISPE's Communities of Practice (COPs), leading activities for the foundation and growth of the Active Pharmaceutical Ingredients (API) COP, Containment COP, and Oral Solid Dosage (OSD) COP. He can be contacted by email: julian.wilkins@pharmaconsultus.com.

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Risk Assessment on Capital Equipment Planning for the Biotech and Pharmaceutical Market

by Mark Mathis

This article presents processes and metrics for identifying and evaluating risks associated with capital equipment planning during the Conceptual Project Planning Phase.

Introduction

Consultants often get involved in the up-front capital assessment of projects that set out to procure equipment packages ranging from small items, like individual pumps and filters, to larger skids and modules. A well thought out plan and risk management approach will help the Conceptual Project Team get the most from their equipment investment, and help to prevent costly mistakes later in the schedule. Purchasing capital equipment is a process. It begins with defining the needs as much as possible, establishing a baseline for which equipment will be defined, and working with reputable suppliers who can commit to the commercial and quality expectations. It is a common mistake to rush a capital equipment list in effort to arrive at a factored estimate of Total Installed Cost (TIC), and then proceed with that information without putting it through a diligent risk assessment process. The very nature of these conceptual estimates is that they are wrought with assumptions and best guess models of what the equipment and plant will look like anywhere from one to two years from concept. This article will discuss the tools and techniques meant to identify and assess risks associated with equipment procurement along with the respective impact to long term project goals.

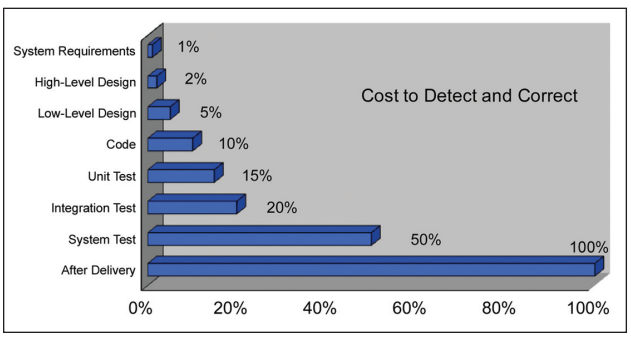

Figure 1. Relative cost of failure.

Relative Cost of Failure

Risk Assessment can be a valuable tool in assessing the relative cost of failure. This is the principal that identifying problems and potential failures early on prevents long-term project disaster. When working with clients, performing the due-diligence required for a solid design basis and a valuable equipment budget must be one of the top priorities. Figure 1 demonstrates that the relative cost of failure increases exponentially as the project timeline progresses.

The goal is simple. Provide a solid technical foundation to capital equipment budgets such that even when the project is complete, anyone can look back and trace the evolution of the design and the budgetary numbers associate with the equipment. This occurs by having the right project team and by implementing risk management and budgeting techniques discussed in this article.

Procurement

To discuss risk assessment with regard to capital equipment, begin by reviewing the procurement process. Procurement is now a multi-disciplined team process that may involve management, purchasing, contractors, vendors, legal, finance, marketing, sales, engineering, technical, and operational people. With the growth of the internet, the basic mechanics of purchasing have become more available to those outside of the Procurement and/or Estimating Group. Access to budget pricing, online quotes, make/model number of equipment, even sample contracts are available for most of the major suppliers. Engineers are being brought in on contract matters, such as liquidated damage clauses and incentives to provide more realistic and historical input on what can and does happen over the life of the procurement cycle. This has

empowered engineers and owners to take more of a direct role in selecting and budgeting equipment for their processes. It also has opened the door to bypassing important parts of the process like risk assessment on critical items and the overall project impact that can result from poorly planned budget. Treating the procurement process as linear, acquiring capital equipment involves the following basic steps - *Figure 2*.

It is recommended to start implementing the risk assessment process at the start of the Estimate Costs Phase. Due to time constraints, the estimating process often eliminates several key steps. The equipment budget will be full of assumptions, necessary to create any sort of foundation given that the design is in its infancy. These assumptions should not be made outside of the core design team. Using contractor services to facilitate the budget development is one thing, leaving it entirely in their hands is a potential mistake. Like all business relationships, contractors have a tendency to have bias toward certain suppliers. This bias should be based upon the manufacturing needs and/or previous experience with certain suppliers, not a tangential and unrelated relationship with a contractor. The contracts between owner and supplier must be good for both sides to be successful, the contractor will not necessarily need to be involved in negotiation.

Preparation and Planning

Projects will always be taking on some risk when estimating equipment need and cost. Part of the mechanics involved include reviewing all layouts, process requirements, and equipment performance criteria carefully. But what to do when this information is lacking?

With a good equipment list, a factored estimate for an existing building (3 to 4.5x total capital equipment budget) to a Greenfield project (5 to 6.5x total capital equipment budget) can be developed to determine Total Installed Cost (TIC). Due to the nature of conceptual design and the lack of detail present, it is recommended to view the equipment list and budget as a fluid animal. Most budgets begin with a process need. A process engineer along with a good process architect can layout the process and start with "paper-doll" activities of placing equipment in and around the new space. Once the space is defined another factor relating current cost/sq ft can be overlaid on the estimate to help justify the numbers. Most important is to consider how equipment will function together. This is where smaller, seemingly less important, equipment items will start showing up in the plan. When discussing the equipment list, walk through an operation and "make a batch." What needs to be permanent? What needs to be portable? If portable, how will it enter/exit the room? How big can it be?

Many companies in other industries use up to a year for their budgeting process to project their capital needs, the pharmaceutical market seldom has that luxury. If there is time in the schedule to map out, design, and properly quote the equipment, the risk will be reduced significantly; however, this is often not the case as projects are constantly up against aggressive drug-to-market timelines.

Start with preliminary planning. ICH Q9 Risk Assessment involves defining the problem to be solved or risk identification.

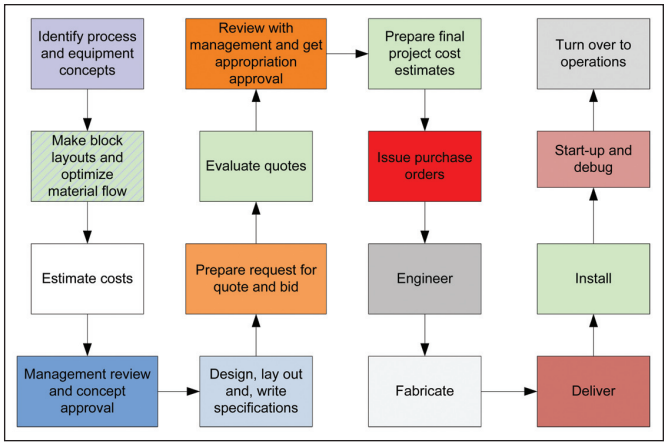

Figure 2. Capital equipment procurement workflow.

The problem in the case of some conceptual capital equipment lists is lack of pertinent design information. Instead of plugging holes with assumptions that are "best guesses," include as much of what is not known in the upfront planning documentation. As an example, if the number of chromatography buffers is still undecided and affects the amount of ports and throughput on the chromatography skid, include this detail in the description or comments on the equipment list. In order to complete the budget with the information on hand, assumptions will have to be made. Agree with the team what areas will require further development and write out objectives on how to arrive at the solution. During this process, identify and evaluate alternatives. Writing a mini-scope to keep the equipment within defined boundaries can help keep people from expanding those boundaries. A project with a changing scope has little chance of meeting any approved budget. Defining the mini-scopes will be helpful in the next phase of Risk Assessment, Estimate Risk.

The entry into the equipment budget may look simple - *Table A*. A rule of thumb can be that anything over $100,000 has a risk assessment performed to establish the scope of supply for future reference. Comments and/or analysis should be specific, yet not overly complex and estimates should include any necessary components for what needs to be measured or reported from the skid. Notice in the above example, there is included both original and current budget price. These columns will be equal at the start of the job. As the project progresses, the original budget column never changes. The current budget column will be fluid and represent the more up-to-date information on pricing and as-purchased cost.

Risk Analysis in Practice

Some of the terms from the ICH Q9 Risk Assessment process have been altered to provide a more practical approach for our industry and the subject matter. To begin a risk analysis, follow these steps:

1. Identify Liabilities: (Risk Identification)

The first stage of a risk analysis is to identify potential liabilities facing the project and/or company's road map. This will be the largest factor in the risk analysis because it can swing

Equipment Tag	Name	Description	Original Budget	Current Budget	Budget Remarks
CHR-001	Chromatography Skid (HIC)	10 inlets, B-trap, 2 RL pumps, liquid filter, 6 way-column valve, auto valves with LS, 1" tube.	$535,000	$535,000	Chrom skid initially estimated with 10 inlets including WFI and Product. Liability: number of HIC buffers required, >6<10. Throughput estimated at 20 lpm.

Table A. Process capital equipment list and budget.

the project budget significantly up or down. As mentioned in the factored estimates, a $100,000 equipment liability can mushroom six-fold against the TIC of the facility. Liabilities may be found in the following categories:

- Process – scale is undetermined leaving many questions around capacities of major equipment
- Operational – lack of SOPs or URS docs for a new or changing facility can leave many operational needs unknown. This can impact disruption to supplies and operations, loss of access to essential assets, failures in distribution, etc.
- Procedural – internal systems around procurement and even equipment specifications are not available or undefined.
- Leadership – lack of competent and trained personnel to properly specify, procure, design, manage, test, and install equipment can lead to lack of insight into budget requirements early on.
- Project – risks of cost over-runs, schedule delays, or insufficient product or service quality, etc.
- Financial – Capital budget appropriation is not finalized or approved.
- Technical – from advances in technology, prior issues with sterility, process failures, etc.
- Natural – liabilities from weather, natural disaster, etc.

To start, run through a list such as the one above to see if any apply to the project or equipment packages being purchased. Secondly, think through the equipment systems and how they function as a collective (transfers, harvests, cleaning, steaming, etc.) and analyze risks to any part of those systems. Talk with other owners and colleagues, try to review lessons learned on similar processes. What was overspent? What was needed later after the facility was constructed? What long lead was overlooked?

2. Estimate Risk: (Risk Analysis)

Once the liabilities have been identified, the next step is to work out the likelihood of the liability being realized and to assess its impact. Note that this evaluation will disregard cases that present advantages to the systems. Though these are important, this article is focused on preventing the negative outcome of such issues.

Let's look at one example of a liability element coming into play mid-way through the project. A common problem is that as the process is further developed, a production support skid is determined as required, such as a portable media/buffer mix skid. There exists a fixed mixing/hold system that is already utilized for the existing plan and a portable skid now frees up resources and allows for more flexibility. Start by making the best estimate of the probability of the event occurring, from 0 to 100%. Let's assume 15%, and multiply this by the amount it will cost to procure and install if it happens. Since the unit is portable, we'll assign $90,000. This gives a rounded value of $13,000 for the risk.

Now as a function of contingency, this can be a very small component of risk. However, if several of these liabilities are on the table, it may make the difference as to whether to include an extra 5% or 10% contingency on the budget. When including contingency on the equipment list, don't be afraid to break down what that contingency represents. Table B is a basic example.

3. Managing Risk: (Risk Evaluation and Reduction)

Once the value of risks is worked out, start to look at ways of managing and/or reducing the risks. When doing this, it is important to choose cost effective approaches – in most cases, there is no point in spending more to eliminate a risk than the cost of the event if it occurs. Often, it may be better to accept the risk than to use excessive resources to eliminate it. Risk may be managed in a number of ways.

By Leveraging Existing Resources or Assets

Here existing assets or resources can be used to counter risk. This may involve changes to existing procedures and systems, changes in responsibilities, improvements to internal controls and accountability, etc. Using the above example of a mixing skid addition, consider existing vessels that may be underutilized or available and modifying them to meet the need. This would significantly lower the impact of the risk cost and help reduce the overall contingency for such events.

Capital Equipment Commercial Summary:		Breakout Cost:
Process Equipment Budget Subtotal:		$ 20,000,000.00
Contingency: (5%)	*Breakdown*	$ 1,000,000.00
Exclusion Risk (1.5%)	$300,000.00	
Operational Risk (1%)	$200,000.00	
Financial Risk (1.5%)	$300,000.00	
Expediting (0.5%)	$100,000.00	
Other (0.5%)	$100,000.00	
Insurance (1%)		$ 200,000.00
Tax Allowance (1%)		$ 200,000.00
Freight Allowance (3%)		$ 600,000.00
Inspections/Testing (1.5%)		$ 300,000.00
Grand Total		$ 22,300,000.00

Table B. Contingency example.

By Contingency Planning

If all other alternatives have been reviewed, decide to accept a risk. The objective at this stage is to choose to develop a plan to minimize the effect of the risk if it happens. By implementing and utilizing a contingency plan, this will allow a quick response, with the minimum project impact. This amounts to more than just allocating dollars, but also defining what steps/action will be taken should the risk occur.

By Investing in New Assets

The risk analysis should give the basis for deciding whether to bring in additional equipment to counter the risk. But what if the overall risk assessment determines several risk scenarios requiring a vessel or a pump or a filter. At this point,consider the path of purchasing a multi-purpose asset that can serve as an option for several risk scenarios. An extra 500 L portable vessel can be a mix tank, addition tank, storage tank, etc. Same goes for items like rotary lobe pumps or filter housings. Having an extra unit not only helps mitigate risk, but serves as a spare parts reservoir for installed, similar equipment.

4. Regular Scheduled Reviews: (Risk Acceptance and Review)

After applying a risk analysis to the appropriate equipment, schedule times to revisit and possibly reevaluate the assessment. This might involve formal reviews of the risk analysis or may involve incorporating available research and information that has come about through the course of the project. As an example, if the cost of a planned instrumentation add-on, such as a refractometer, is unknown, and you've received the budget quote from the supplier, revise the data accordingly. Maintain a list of all the risks that were evaluated along with project impact for cost, schedule, operations, and any other areas that may be affected - *Table C*. Once the risk is determined as expired, remove from the list and funnel the cost back into other contingency areas.

Risk Analysis Primary Benefits

The primary benefit of risk analysis is that it allows the project team to examine the risks that the organization will face. It is based on a structured approach to thinking through liabilities, followed by an evaluation of the probability and cost of events occurring. For most of us, the emphasis is on cost effectiveness and damage control. Risk management involves adapting the use of existing resources and/or assets, contingency planning, and good use of new resources.

Selecting the Right Team

For major equipment, the project director, project manager, or person assessing the conceptual budget should put together a project equipment plan for each unique package. A package is defined as a group of like equipment such as vessels, agitators, or bioreactors. Major capital projects are usually assigned to a project manager or project engineer based on project size. This person defines the problem, determines the project plan, and handles schedules and budgets. This would consist of the following: process justification, specification/RFQ package preparation, bidding, contract administration. If applicable, this person should liaise with the engineering firm each step of the procurement process and should represent the buyer's interest. Outsourcing this step of the process may return a more detailed and defined equipment list, but it would likely be from a previous and possibly unrelated project and not fully represent the needs of the owner's plan.

To Sole-Source or Not to Sole-Source

The question that often comes up first is how to select those items that will be bid out and those that will be sole-sourced to suppliers. The pharmaceutical/biotech industry differs slightly from others in that a great majority of the large capital equipment purchases are custom equipment. The industry is changing rapidly. Skids that were always custom are now available as Commercial Off-the-Shelf (COTS) items. There are suppliers now that offer a chromatography system that can be ordered by model number.

This sometimes eliminates a traditional sole-source methodology which would sole source those items with only a single supplier. While the pool of suppliers is shallow, there are at least a few that will be candidates for even the most challenging custom process skid. There are also times whereby manufacturers send requests for sole source purchases that describe an item made only by one manufacturer; however, the item is distributed and readily available from many different suppliers. This would be a matter of locating a supplier rep, usually one with regional presence to the facility. This type of equipment has a sole manufacturer, but not a sole supplier.

Since sole source items are exempt from the formal bidding process, all requests for sole source should be submitted to the Procurement Lead along with justification for such action. There are contractual considerations for these type of purchases. There are projects where the client's philosophy is that as long

Capital Equipment Risks by Area			
Risk Assessment Item	***Probability***	**Cost**	**Cost with Probability Factor**
Fermentation			
Quantities of add tanks are not fully defined.	25%	$87,000.00	$21,750.00
Inline HTST skid be required for media feed.	15%	$176,000.00	$26,400.00
Additional liquid filter 0.1 required for Bioreactor.	50%	$18,790.00	$9,395.00
Purification			
Additional buffer inlets on 2 HIC chrom skids.	35%	$31,450.00	$11,007.50
Viresolve skid may be required.	40%	$235,000.00	$94,000.00
Production Support			
Portable CIP skid needed for media prep area.	25%	$215,000.00	$53,750.00
Transfer panel needed for harvest.	35%	$89,000.00	$31,150.00
Grand Total		**$852,240.00**	**$247,452.50**

Table C. Capital equipment risks by area.

When to Sole Source:
1. There is no functional equivalent to the equipment required from the supplier.
2. Time is of the essence and a longer procurement schedule is not possible.
3. Where the compatibility of equipment, components, accessories, software, replacement parts or service is the primary consideration.
4. Where a sole supplier's item is needed for trial use or testing.

Table D. When to sole source.

as there is more than one potential bidder or offeror for the equipment item then there is no justification for a sole source determination. This article explores the rational for considering sole source, even when there are multiple suppliers. But first, Table D illustrates some examples of circumstances which could necessitate a sole source purchase.

A range of pros and cons come into the picture at this point and having worked with multiple small and large scale projects, Table E provides a few of the major points to be considered. Assessing risks for sole sourcing materials can be broken down into some basic queries for each item considered. Figure 3 illustrates one tactic to identifying equipment as sole-sourced.

This practice is especially effective in conceptual estimating when there is very little information available. By identifying items to be sole-sourced early, it is easier to leverage the advantages of cost and time savings for the overall project budget. Once sole-sourced items are agreed, these vendors can be targeted early to participate in the design and help polish out specifications developed early on in the job.

Sole Sourced Pros:	Sole Sourced Cons:
Value in continuity with common supplier	Probability of higher cost by removing competition
Time off of equipment schedule by removing bid cycle and analysis (3 to 5 weeks)	Less incentive for supplier to perform any better than last project
Higher probability of known end product especially if replicated from previous purchase	Supplier resource allocation can be overlooked by not competitively bidding schedule
Time saved on validation documentation	Less flexibility for making changes to a fixed supplier design
Advantage of same or similar project team and structure within a supplier's organization (less of a learning curve)	Lack of access to innovation from other suppliers
Leverage on potential future purchases	
Greater potential for meeting schedule with lower odds of scope creep	

Table E. Sole source pros and cons.

Assessing Risk for Contract Manufacturing Facilities

When estimating for CMFs, consider the flexibility required to meet the needs of several projected drug products. First, establish a basic process philosophy like mammalian cell culture or bacterial fermentation. Then establish size and scale for operating capacities. Decide on initial footprints with expansion possibilities identified. The challenge comes from what is being planned to put in the space, and how that equipment will hold up for five or 10 or 15 years of changing operations.

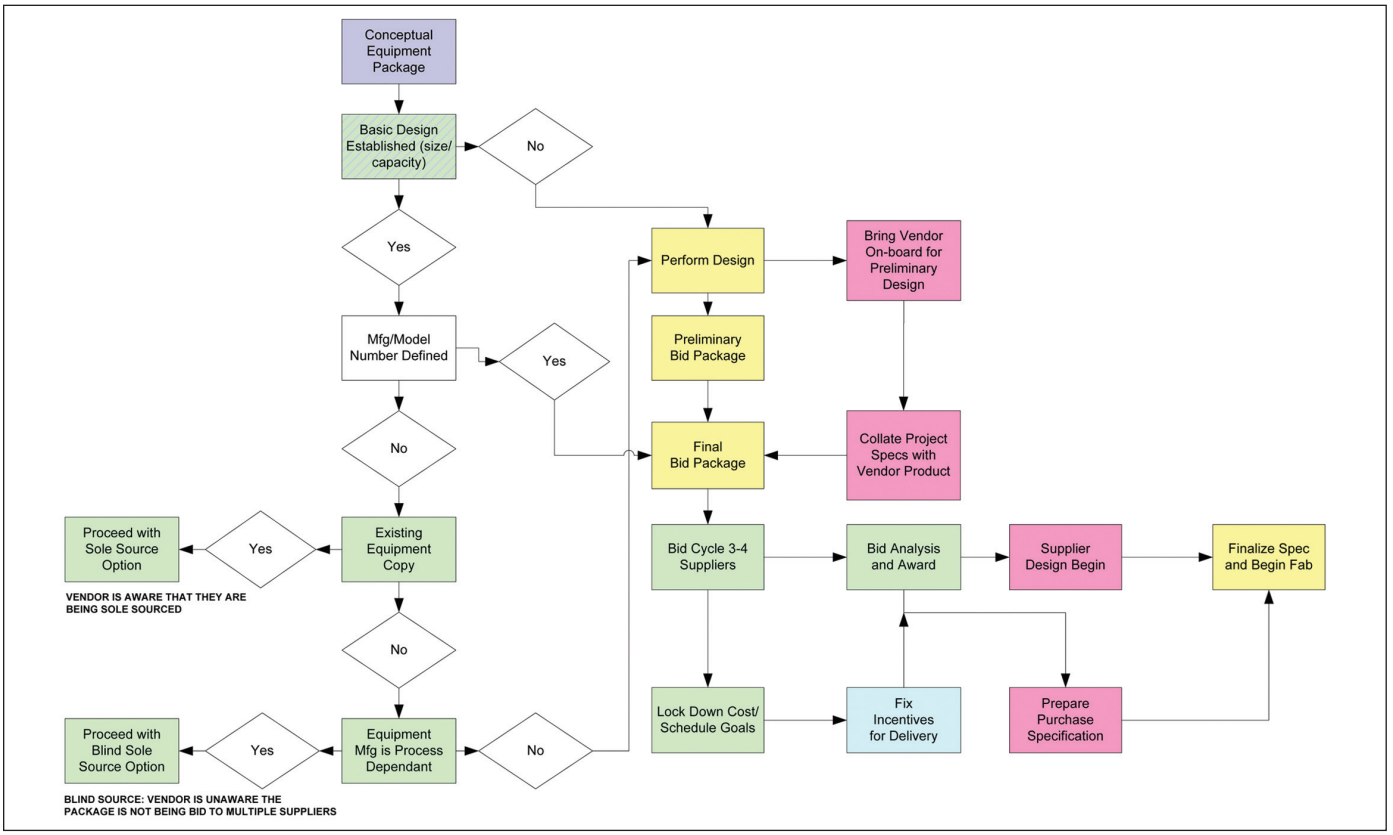

Figure 3. Sole source logic flow chart.

The components and considerations experienced in budgeting CMFs were now extending to more boilerplate facilities for established drug-lines. Options for SIP capability, built in by-pass lines, tank jackets for non-temperature controlled vessels, extra inlets for chrom skids, dual operating volumes for UF and bioreactor systems are being considered to make sure there is as much reasonable flexibility built into the equipment's future. Suppliers are now being challenged to squeeze even more into smaller footprints and told to make everything at least movable if not portable, as much as possible.

Methods of Budgeting

Since a manufacturer's facility is always highly unique and will tailor its needs toward whatever multi-product lines that will be continued within its walls, it is suggested to take more of a macro approach to assessing risk. The ideas presented here should have application in any type of large-scale project whether it is planned as multi-product or not. First, break down the major categories of capital equipment. For now, focus on just the process items and leave utility equipment for later. Major categories are as follows:

- COTS items (with model numbers predefined and no custom changes)
- Stainless Steel Vessels
- Custom Process Skids (Reactors, UF, Chroms, etc.)
- Custom Process Modules (Buffer Prep Tanks, Media Prep Tanks, Chemical Storage)
- Production Support Equipment (Heat Exchangers, Pumps, Temperature Control Systems)

These items all have several things in common with one another. They all require freight, taxes, consumables, testing, and in most cases, options that are required or specific to the process.

Freight

A common oversight on any equipment budget is the exclusion of freight and associated parameters like FOB locations, insurance, transit time, and crating. A good rule of thumb for an overall equipment budget is 3%. This should allow enough conservative flexibility in the budget to allocate slightly more or less of this amount to individual packages. Keep this sum outside of the individual budgets and assign amounts based on need at purchase. It may be that the package budget has already accommodated the expense of freight.

Taxes

Another oversight or more accurately, "misunderstanding," is the tax component. This will vary by state, but in most states there are favorable exemption clauses that on average are between 1% and 2%. If you don't know what your state's tax rate is, suggest using 1.5% as the estimate on the equipment list in total and once again keeping that allowance separate and allocating as needed.

Options

Here in lies a challenge. How to budget or plan for options whose use may not be apparent. Start by breaking out the equipment categories.

Commercial-Off-The-Shelf (COTS) Items

Budgeting options for COTS items should be a straight forward process. If the catalogue or model number with cost is already identified, review what has been purchased in the past or what the projected need is and budget accordingly. If options are available and the project team is not in a position to select which ones are needed, assign a package contingency and move forward. The overall equipment budget will have a contingency also.

Stainless Steel Vessels

Tanks are relatively simple. Take a standard tank budget for a 1000L 20Ra/EP vessel with an average real estate of nozzles and ports and an outlet valve. Start by taking into consideration the basics of tank design.

Temperature Control?

When asked for a budget from a supplier, make sure to clarify whether or not this vessel is being used to maintain temperature of the contents. In general, it is recommended to include in the budget, insulation and a jacket. Here is why:

Standard 1000L Vessel ($30,000) + Insulation (7%) + Jacket (11%) = $35,400.00

For an 18% cost adder, the flexibility and usefulness of this vessel have been increased ten-fold.

How Many Ports?

As far as nozzles go, the quantity of ports should be a mix of what is needed for the process balanced with how much can fit on the vessel itself. Keep in mind that as the quantity of nozzles goes up, the geometry and heat transfer area is effected. Here are the major items to consider and suggested cost factors:

Standard 1000L Vessel ($30,000)

Normal # ports 1.5% of nominal volume = 1.5% of 1000(L) = 15

Additional ports required should add 3% to total vessel cost

Ports greater than 15 = 3 = $30,000 × 3 × 0.03 = $2,700.00

When adding ports, consider whether there is room left for a traditional manway or handhole. If this is a concern and a removable head is required, an additional 15% of estimated cost should be added to account for the higher head thickness, gasket and clamps.

Custom Process Skids

These items may seem intimidating at first because not only are there a lot of liabilities, these are also some of the highest cost equipment on the list. For most process skids, the following formula applies for budget. Here are some basic strategies and case examples to use:

Case Example: Basic Ultrafiltration System

1. Identify Largest Throughput: Small (<15l pm), medium (>15l pm < 40l pm), large (>40l pm <100l pm)
   a. This helps determine the size of the support piping and associated components. Examples of budgets for each of the skid sizes includes a sanitary pump in the cost.
      i. Small = $37,500
      ii. Medium = $68,000
      iii. Large = $90,000
2. Identify Primary Capacity: Capacity of filter membrane – small (<5 m2), medium(>5 m2 <40 m2), large (>40 m2 <100 m2)
   a. This helps determine overall nominal process capacity of the system. It also helps to disassociate the membrane from the skid in the event that this item is provided separately. For UF, adjust the factors based upon hollow fiber, Code VII housings, or square cartridge. All of these styles are priced out and easily found through the rep or on the internet.
   b. For this baseline, assume a single Planova disposable at a budget of $24,500.00
3. Identify Number of Primary Monitored Points: 13
   a. 2 flowmeters, 3 PITs, 2 Temperature, 2 UV, 2 Cond/pH, 2 Undecided
   b. Multiply number of standard monitored points × $1,500 for a total installed instrument cost. 13 × $1,500 = $19,500
   c. Based on size, provide estimates for each planned component
      i. $9,000(2) + $2,300(3) + $1,900(2) + $28,000(1*) + $2,500(2) = $61,700 for instrumentation + $19,500 for points = $81,200
      *Notice the combined budget for 2 UV meters, knowing that only 1 display is required.
4. Controls
   For controls on a local PLC system, budget as follows:
   a. Basic Panel = $5,000 + (Number of Monitored Points × $500) + OIT + Processor (Allen Bradley in this example)
   b. $5,000 + $6,500 + $5,500 = $17,000
5. Specialty Items
   a. Here is where to include specialty items outside of the norm. For these purposes, include a refractometer at $29,000.
6. Throughput + Capacity + Instrumentation Points + Controls + Specialty Items = Baseline Budget
   a. $68,000 + $24,500 + $81,200 + $17,000 + $29,000 = $219,700.00 or ~$220K

Custom Process Modules (Buffer Prep Tanks, Media Prep Tanks, Chemical Storage)

Now for more complicated systems, there may be some variability in approach. Hold these larger, more cost intensive equipment purchases to a custom model to make sure to have a solid number to go along with the planned design. However, if this method is applied to the same system, for example, a bioreactor budget, do so by breaking it down into its five primary sub-systems: Vessel, Gas Module, Temperature Control, Addition Vessels, and Exhaust. Then take each subsystem and develop a baseline budget which totals up to the whole. If certain systems have a more intensive controls portion, take that out of the equation and call it out separately.

With the advent of modular design, the industry took a sharp turn back in early 2000. It seemed that every client encountered was interested in the concept and some would frequently get caught up in semantics. A skid is not a module, a module is in fact a collection of skids or subsystems. The most common module is the collection of like operating vessels with a uniform set of parameters and functionality. For this example, use a Buffer Hold Module.

A Buffer Hold Module is now in the scope of the Conceptual Capital Equipment budget. The module is there is serve a uniform purpose with multiple subsystems achieving a common operation. When budgeting modules, take the counterintuitive approach of breaking out the subsystems and first categorizing individually.

Number of Subsystems (6 tanks = 6 subsystems) + Overall Controls and Interface + ESA

1. The first item, subsystems, can be approached just as the skids above. Apply the formula: **Throughput + Capacity + Instrumentation Points + Controls + Specialty Items = Baseline Budget.** All of these systems are assumed to come non-programmed by supplier so leave out the additional automation engineering for this example.
2. Overall Controls and Interface is to account for any OIT that may be intended to serve as a Suite interface for all subsystems.
3. ESA – Electrical, Structural, Architectural. These components are unique to modules in that it is rare to see much of it on any other equipment item or skidded systems.
4. A budget may look like this:
   Buffer Hold Module with (6) 2,500L Vessels
   Subsystems($125,000)(6) + Overall Controls and Interface ($50,0000) + Electrical ($13,000) Structural ($20,000) Architectural ($15,000) = $848,000

General Ways to Reduce Risk when Estimating

Here are some common sense ways to mitigate risks for any capital project. These are staples of lessons learned documents and should be considered as part of the planning process.

Stainless Steel and other Appreciations

Having covered the basics of budgeting with the usual cast of characters in an equipment list, here are some factors that can greatly influence the cost estimate and ultimately risk. Start with stainless steel. The cost of stainless has crashed many budgets, due to ever fluctuating market conditions and the supply/demand of the individual suppliers. If planning a budget in advance of procurement by any longer than 60 days, include an allowance for all stainless steel based equipment items of 1%/month. This will give some flexibility to what is certain to be a liability factor in the plan.

Fabrication Windows

Another factor to consider is fabrication windows for the long

lead equipment items. If engaging a supplier under contract for a specified due date, and procurement of the system is delayed, there will be incurred cost to accelerate the schedule to meet the projected end date. This sounds like planning for the worst, but think of it this way: if there is an average number of equipment packages, say 20, expect that 10% may go off schedule due to design delays, weather (Katrina), or just plain bad luck. If this 10% is taken into consideration, that would amount to two of the packages. If these two packages are in excess of $500,000 total each, and must account for delays (or acceleration of the suppliers schedule at a cost), then consider including a 5% variance for this scenario not to exceed $100,000. That amounts to $50,000.00 total allowance. This pays for overtime, unexpected travel, and accelerated shipping cost. If there are more than 20 packages, this can happen to at least two of them.

Testing

Testing is frequently overlooked and underestimated. A common mistake is to assume that a large skid or module would only require one to two trips for the FAT and does not take into consideration testing or inspection of the subcomponents. To make valuable use of the time, and time is of the essence, then getting in front of potential equipment problems is a must. This would include large scale pumps, exchangers, and vessels – all inspected at the shop of origin. These are no longer the days of $2,000 plane tickets. It is possible now to inspect an item halfway across the country and sometimes make it home in the same 24 hour window. A good approach is that it is better to have and not need than need and not have. Suggest a 1% of total equipment budget allowance for testing. For a $20 million budget, this gives $200,000 for expenses, time and overhead required for testing.

Bidding Requirement

When preparing a project for bidding to potential contractors, a typical bidding requirement checklist is useful. Purchasing staff begin significant involvement at this stage and continue throughout the contract period. Keep the bidder's list up to date. Low retention rates in the pharmaceutical industry extend to the suppliers as well as the manufacturers. Don't assume that this will get the same personnel or same service for that matter, just because the contract is with the same supplier.

Used Equipment

Purchasing used equipment is tricky and can sometimes seem like a wild goose chase. Just finding the equipment that meets the specification is hard enough. To then expect that it can be tested and installed as operational is another long and labor intensive exercise. If the equipment is out there, and it is in good condition and available, then the capital available to make the purchase is required – sometimes on the spot. Be prepared to write a check for the full amount after the inspection. Below is a checklist of items to consider when purchasing used equipment.

- Freight costs for new and used equipment will be nearly equivalent. Tax can be planned as equal also.
- Installation costs for used equipment will be equal or slightly more than new equipment, depending on how the equipment is removed. Removal cost will be another line item to have in the budget as the owner may or may not accommodate this. Try to use the same team that removed the unit to install the unit at the owner's facility.
- The used equipment should be less than half the cost of new equipment. Schedule is not everything and there must be value in taking this route.
- Analyze cost of new equipment versus used equipment plus rebuild requirements. Always perform a thorough inspection.
- Network with used equipment dealers. There are not many in the industry so this should not be difficult.

Conclusion

In closing, this article has discussed several methods of risk assessment along with the metrics to manage them. There are several different ways of identifying risk and the formulas to assign cost and other repercussions that have been reviewed. Developing a plan, assembling the team, identifying risk, and working with good suppliers will pave the way for a successful and useful equipment budget and one that doesn't expire two months into the job, documents a solid baseline, makes clear all assumptions, and mitigates risk. Keep an open mind and stay on the lookout for new and improved ways of adding confidence to the conceptual budget.

References

1. FDA, ICH Q9: Quality Risk Management CDER Advisory Committee for Pharmaceutical Science (ACPS) Presentation (online), October, 2006.

About the Author

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Update on ISPE's PQLI Program

by Dr. Kate McCormick, ISPE European Education Advisor

There were two sessions on the Product Quality Lifecycle Initiative (PQLI) during the Annual Meeting in Orlando, FL, USA in November.

Newly-appointed ISPE board member Joe Famulare chaired the first session on PQLI for Pharmaceutical Quality Systems. He previewed the work of two task groups working in parallel: process performance and product quality monitoring; and change management. Delegates were told that "the cake is not fully baked" and that the working groups were keen to receive questions and comments on the approaches being taken.

Topics covered included the development of a Good Practice Guide on Control Strategy; the way in which issue identification and mitigation can drive continual improvement; and approaches to the change management system that can drive continual improvement over the product lifecycle.

The morning concluded with a regulatory perspective from Tara Gooen (US FDA) who presented regulators' experiences by addressing the question "how good are our measurements?"

In the afternoon, Chris Potter chaired the session on Implementing ICH: Product Design, Development and Realization, a Science- and Risk-Based Approach to Implementation. Following a review of the PQLI Road-Map which had recently been published and an update on the Illustrative Example, delegates heard presentations on criticality, design space, and control strategy.

Tara Gooen rounded off the afternoon's session with a presentation aimed at encouraging early adoption of the risk-based approach, including a number of very useful case studies.

Concludes on page 2.

The New and Improved Pre-Approval Inspections Program

by Rochelle Runas, ISPE Technical Writer

The Regulatory Town Hall Forum held 8 November 2010 at the 2010 ISPE Annual Meeting in Orlando, Florida, USA focused on current and emerging issues related to Pre-Approval Inspections.

US FDA Pre-Approval Inspections (PAIs) may be conducted before the Agency approves a new drug to be marketed in the US. These inspections occur following FDA's receipt of an NDA or ANDA and focus on the manufacture of a specific drug. PAIs are designed to verify the accuracy and authenticity of the data contained in these applications to determine that the establishment is following commitments made in the application. PAIs also assess whether the establishment can manufacture the product in the application in conformance with GMPs.

Overview – FDA's PAI Program Revisions and Trends

Tara Gooen, Team Leader, Office of Compliance, FDA/CDER/DMPQ, gave an overview of revisions and trends in the FDA's PAI Compliance Program to align the program with the "Desired State" as part of the FDA's Pharmaceutical Quality for the 21st Century initiative. Specifically, in May 2010, the FDA carried out its first major revision of its PAI Compliance Program since the early nineties, laying out a number of inspection scenarios based on risk, the application filing, site, and reflecting ICH Q8 (R2), Q9 and Q10 principles. The FDA also covers small and large molecules for the first time.

Gooen reviewed related revisions to the FDA Pre-Approval Inspections Compliance Program Guidance Manual (CPGM) – essentially the SOPs used by investigators which provides valuable insight into what investigators will be looking at during an inspection. The revisions reflect enhanced internal collaboration among FDA staff, including the implementation of a Knowledge Transfer Program to produce product and process knowledge from CDER to the ORA for inspection preparation for high risk/complex products and processes; international collaboration; integration of a BLA pre-license/approval inspection program (most of the program is handled within CDER); and samples are collected for-cause only.

The following criteria may be grounds for a priority inspection:

1. Establishment is named in an application to the FDA for the first time, including establishments that have never been inspected or have been inspected only for non-application drugs
2. First application filed by an applicant (for coverage of finished dosage manufacturing and testing)
3. First ANDA filed for an approved drug (for coverage of finished dosage manufacturing and testing)
4. Finished product contains a New Molecular Entity (NME) (does not apply to supplements)
5. Finished product content assay has a narrow range (e.g., 95 to 105% labeled strength for narrow therapeutic index drugs) or drug is expected to require titrated dosing (does not apply to supplements)
6. Finished product or API is manufactured by a substantially different manufacturing process or dosage form than previously covered at the establishment
7. API derivation is high risk (e.g., API is derived from animal tissues) or

Continued on page 3.

...PQLI Program

Continued.

A key feature of the day was the lively Q&A sessions, of which the following is merely an extract:

- Christine Moore (US FDA) told delegates that training of FDA recruits is continuous and extensive, with many internal and external programs to increase reviewers' understanding of QbD. The number of applications involving QbD is increasing and there is a continuing need for recruitment. Tara Gooen added that additional efforts were being made to bring manufacturing knowledge in-house. FDA is also hiring across a wider range of disciplines, especially, statisticians and engineers.
- Joe Famulare reminded delegates that ICH Q8, Q9, and Q10 are optional additions to GMP. There was never any intention to use them to harmonize GMP, but to recognize where there are similarities. Regarding the possible harmonization of ICH Q10 and ISO 9000, he stated that the Q10 committee had made a clear distinction between continuous improvement of product and process and continuous improvement of the Quality Management System.
- It was pointed out that a key challenge is to encourage scientists to think about the data. It was agreed that companies need both appropriate tools and practical examples. One suggestion was to use teams with product stewards who evaluate the data and find opportunities for improvement. The product steward model exists in various companies and works well; the steward stays with the product from development through the entire lifecycle.
- There was a discussion on how much of the data should be maintained and for how long? One delegate responded that they do not erase data, instead keep it for a long time. There is a need to go back on occasion to find something that's happened; sometimes this can be well in the past. The bottom line is that data should be available readily. Experience shows there are often questions on raw data which need to be accessed.
- The question was raised: are we running the risk of making life more complicated rather than simpler? A response from industry was that it is still early in the process. The regulatory response was that FDA is not interested in over-complicating things, but they are very concerned about risks to product quality; hence the focus must remain on patient safety.
- It was pointed out that it is impractical to look at all data, but experiences shows that aspects thought to be unimportant may turn out to be critical during different stages of the lifecycle. There is a need for real examples of what should be looked at during different stages of the lifecycle.

That final point echoed what was said by many of the speakers during the day: contributions are being sought in the form of examples or case studies that can be incorporated into the body of knowledge.

10th Anniversary of Japan Affiliate

The ISPE Japan Affiliate is pleased to announce its 10th Anniversary Annual Meeting to be held from 13-16 April 2010 at Tower Hall Funabori, Tokyo, Japan. The program will include two days of presentations by domestic and international industry leaders, workshops, networking reception, plant tour, and golf outing.

Online registration is available through the ISPE Web site (www.ispe.org) in the Global Events section. Don't miss this unique opportunity to share in the anniversary celebration, learn about the Japanese biopharm industry, and experience the culture of the Land of the Rising Sun.

Becoming a CPIP™

The journey to becoming a CPIP can go at the pace you desire. Eligibility applications are accepted at any time and exam dates occur twice a year. ISPE-PCC has a downloadable Study Guide available to assist candidates in preparing for the examination. ISPE Training offers CPIP Online Learning courses as well. To find out more, visit the ISPE Professional Certification Commission (PCC) Web site at www.ISPE-PCC.org.

Exam Dates

7 March – 15 April 2010
6 September – 14 October 2010

...Inspections Program

Continued from page 62.

the intended use has significantly changed (e.g., API previously used in non-sterile product is now intended for a sterile drug product)

8. Numerous application submissions or certain site/process/product changes that are expected to pose significant challenge to the state of control of the facility or process
9. Profile class status of application product or API is "unacceptable" or not updated via a site inspection within the past two years (three years for control laboratories and four years for packaging and labeling), for original applications or significant pre-approval CMC supplements

Inspectional coverage is focused on an evaluation of three areas:

1. Readiness for Commercial Manufacturing (consisting of five parts: investigations/trends, material handling, contamination, procedures, process feasibility)
2. Conformance to Application
3. Data Integrity – A Data Integrity Audit with the possibility of FDA action against companies that commit data fraud or provide false information to the agency.

Gooen said the major reasons for a PAI withhold recommendation between 2003 and 2009 were:

- Pending enforcement action/previous deviations persist
- Firm not read/drug not made here/facility withdrawn
- Insufficient development data/production/process controls
- Inadequate lab controls
- Inadequate QA functions

For More Information

For further coverage of the Regulatory Town Forum held at the ISPE 2010 Annual Meeting, including articles on an Investigator's Perspective of the New PAI Compliance Program; ONDQA's Perspective on Reviewers on Inspection; and an Industry Perspective on a Joint Inspection Experience, visit http://www.ispe.org/pharmaceutical_engineering. In addition, the following sites are available:

- FDA Pre-Approval Inspections Compliance Program Guidance Manual (CPGM): http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm071871.pdf
- Division of Manufacturing and Product Quality: cGMP Subject Contacts as of May 12, 2010: http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm
- Questions and Answers on Current Good Manufacturing Practices (cGMP) for Drugs: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124740.htm

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International

International Operation Combats the Illegal Online Supply of Counterfeit Medicines[1]

Forty-five countries across the globe have taken part in an international enforcement operation targeting the online sale of counterfeit and illegal medicines to raise awareness of the dangers of buying medicines online. Operation Pangea III ran between 5-12 October and resulted in 76 people either arrested or placed under investigation across the globe. The operation is the largest internet-based enforcement action of its kind to date and involved IMPACT, the World Customs Organisation (WCO), the Permanent Forum of International Pharmaceutical Crime (PFIPC) and the Heads of Medicines Agencies Working Group of Enforcement Officers (HMA WGEO).

Australia and Canada – Reciprocal Recognition of Manufacturers' Quality Systems[2]

The Therapeutic Goods Administration (TGA) and Health Canada announced that the Memorandum of Understanding (MoU) on reciprocal recognition of quality management system (QMS) certificates for medical device manufacturers is now operational. This action follows the signing of the MoU in June 2007 and the completion of a rigorous confidence building exercise between the TGA and Health Canada's Health Products and Food Branch (HPFB). This exercise confirmed the comparability of the two regulatory systems in assessing a manufacturer's quality systems.

Under the MoU, Australian and New Zealand manufacturers of medical devices can export products to Canada and Canadian manufacturers of medical devices can export products to Australia without the need for duplicate assessments of the QMS of medical devices. Similarly, QMS certificates issued by a Health Canada and TGA recognized Registrar participating under the MoU will be recognized by the TGA, and taken into consideration as part of an application for a Conformity Assessment Certificate issued by the TGA.

Audit of the Estonian State Agency of Medicines by Health Canada Completed with Positive Conclusion[3]

The audit in the Estonian State Agency of Medicines was conducted in the framework of Mutual Recognition Agreement (MRA) between the European Community and Canada, Sectoral Annex on Good Manufacturing Practice. Health Canada has concluded the equivalency of systems in place in Estonia and in the State Agency of Medicines.

US FDA and Health Canada – Completion of the Pilot Multipurpose Audit Program[4]

Health Canada and the United States Food and Drug Administration (U.S. FDA) announce the successful conclusion of the pilot Multipurpose Audit Program (PMAP). Initiated September, 2006, this pilot was designed to evaluate the effectiveness of performing a single third party inspection/audit of medical device manufacturers' quality systems.

Eleven joint audit/inspections were performed under the pilot, of which ten were assessed for program benefit. The data suggests that joint audit/inspections result in a measurable savings of time-in-facility for those medical devices manufacturers that took advantage of this voluntary program. Savings of time in person-days for the majority of audits/inspections ranged from 25 to 58% with an average of 33% less total time spent at the facility when compared to the estimated combined time of previous audits/inspections performed individually to satisfy the respective regulatory requirements of Health Canada and the FDA. The lessons learned from the pilot will serve to improve the interaction of both regulatory bodies with Auditing Organizations (AOs), as well as with each other, and streamline the procedures by which qualified medical device manufacturers can take advantage of similar joint inspection/audits.

Both Health Canada and the FDA are committed to continued progress toward a medical device single audit program. While this program is being developed, an update to the Questions and Answers9 document on the PMAP will be published, along with the joint final report on the pilot as a record of what was learned.

China's SFDA Deputy Commissioner Wu Zhen Meets Associate Assistant Deputy Minister of Health Canada Health Products and Food Branch[5]

On 25 November 2010, Catherine MacLeod, Associate Assistant Deputy Minister of Health Canada Health Products and Food Branch, and her entourage came to the State Food and Drug Administration (SFDA) to take part in the 2010 China-Canada High-level Meeting. SFDA Deputy Commissioner Wu Zhen attended and chaired the meeting. Both parties made in-depth discussions on the 2010-2013 China-Canada Regulatory Cooperation Action Plan, the supervision on drug, medical devices and natural health products, and reached agreement on the relevant cooperation programs. Major leaders and relevant officials of SFDA's Department of Policy and Regulations, Department of Drug Registration, Department of Medical Device Supervision, Department of Drug Safety & Inspection, Bureau of Investigation & Enforcement, Department of International Cooperation and National Institute for the Control of Pharmaceutical and Biological Products attended the meeting.

Japanese Ministry of Health, Labour and Welfare (MHLW) and PMDA concluded Confidentiality Arrangement with the Swiss Agency for Therapeutic Products (Swissmedic)[6]

This agreement confirms that MHLW will protect information Swissmedic considers confidential or non-public.

Heads of Medicines Agency

Heads of Medicines Agency Adopts New Strategy[7]

The Heads of Medicines Agencies (HMA) has adopted a new strategy for 2011-2015 at the HMA meeting in Antwerp on 25 October 2010. The key themes of the strategy are: safeguarding

public and animal health; supporting innovation; and further improving the operational efficiency of medicines authorization by the decentralized and mutual recognition procedures.

PIC/S

US FDA and Ukranian SIQCM Join PIC/S[8]

At its last meeting in Kuala Lumpur (Malaysia) on 8-9 November 2010, the PIC/S Committee invited the US Food and Drug Administration (FDA) and the Ukraine's State Inspectorate for Quality Control of Medicines (SIQCM) to join the Pharmaceutical Inspection Co-operation Scheme as from 1 January 2011. The FDA will become PIC/S' 38th Participating Authority while SIQCM will become PIC/S' 39th Participating Authority.

Europe

Denmark

Danish Medicines Agency Publishes Implementation of New Validation Rules for Electronic Exchange of Adverse Reaction Data[9]

Companies which report adverse reaction data to the Danish Medicines Agency were advised that on Monday 11 October 2010, it will be implementing the updated (ICH E2B (R2)) validation rules for the exchange of E2B files, which entered into force on 1 June 2010.

The validation rules are to ensure the Agency receives correct and adequate data when an adverse reaction report is submitted to them. If a report does not comply with the validation rules, an error message advising in detail what caused the error will be sent.

Estonia

Estonian Statistics on Medicines 2006-2009 Published[10]

The State Agency of Medicines publishes the book annually and it gives an overview of the consumption of medicines in Estonia using the methodology of defined daily doses. In 2009 the consumption of medicines decreased by 4.5% calculated in defined daily doses. Most of the major drug classes showed a decrease in consumption, including antiulcer, antithrombotic, cardiovascular, antibacterial, non-steroidal anti-inflammatory, psychotropic and anti-asthmatic drugs. Until 2009 the consumption of drugs has increased every year since 2001 and in 2005 to 2008 the increase was especially remarkable.

European Union

Summary of the Annual Report of the European Medicines Agency 2009[11]

The European Medicines Agency published a document with highlights of its 2009 annual report at http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2010/10/WC500097463.pdf. Some of the issues it addresses include: Improving the effectiveness and efficiency of the Agency's core activities; Consolidating the Agency's international strategy in the light of global challenges; Strengthening the European medicines network; Improving the safety-monitoring of medicines; Implementing and operating the Advanced Therapies Regulation and other new legislation; Fostering transparency, communication and the provision of information; and Contributing to improved availability of medicines.

European Medicines Agency Management Board Adopt New Policies on Handling of Conflicts of Interests and on Access to Documents[12]

The board endorsed the new EMA policy on handling of conflicts of interests, introducing a more efficient, robust and transparent process ensuring that scientific committee members and experts participating in the Agency's activities have no interests in the pharmaceutical industry which could affect their impartiality.

The board endorsed a new policy that defines how the EMA deals with written requests for access to documents related to medicines for human and veterinary use originated, received or held by the Agency (i.e. reactive disclosure). The policy also sets out how the Agency in future will proactively disclose such documents. This policy takes into account the outcome of the EMA public consultation and recommendations made by the European Ombudsman and will ensure the widest possible access to EMA documents. Some documents or part of them may have to be redacted prior to disclosure, to protect commercially confidential information and personal data. When responding to requests for access to documents, the Agency will apply the principle of proportionality to avoid jeopardizing the performance of the Agency's core tasks.

European Medicines Agency Publishes Mid-Year Report 2010 from the Executive Director (January-June 2010)[13]

This mid-year report from the Executive Director to the Management Board is intended to provide an interim overview of the Agency's activities and performance, based on the objectives and targets set out in the Agency's work program 2010. In terms of progress on priorities, the majority of activities are on track. Workload in general is as forecast, although with variation from forecasts in some areas. The budget situation for 2010 is good: revenue and expenditure are on target.

Recruitment Procedure for New Executive Director of the European Medicines Agency Started[14]

A vacancy notice announcing the recruitment of a new Executive Director for the European Medicines Agency has been published. Interested candidates had until 24 November 2010 to submit their application to the European Commission. The vacancy announcement, together with all relevant information and instructions, is published in the Official Journal of the European Union. Thomas Lönngren, the current Executive Director, left the Agency on 31 December 2010, following the expiry of his second five-year mandate.

Appointment of an Acting Executive Director[15]

The second term of office of Thomas Lönngren as Executive Director expired

on 31 December 2010. On the basis of the current timing of the selection and nomination process, the next Executive Director will not be in place until after that time. At the time of writing it is estimated that this interim period may be approximately six months. Existing internal delegation arrangements relating to short-term and ad hoc absence of the Executive Director are in place, but the Management Board should appoint an Acting Executive Director for the interim period.

European Medicines Agency and Massachusetts Institute of Technology Launch Joint Project on Regulatory Science[16]

The European Medicines Agency and the Massachusetts Institute of Technology's (MIT's) Center for Biomedical Innovation (CBI) and Center for International Studies (CIS) are launching a collaborative research project with a focus on enhancing regulatory science in pharmaceuticals.

The data and recommendations from this project are expected to link to implementation of the Agency's Roadmap to 2015 and the CBI's New Drug Development Paradigms (NEWDIGS) research programme. The project will explore the feasibility of, priorities for, and practical considerations of implementing demonstration projects on some of the issues addressed during the course of the research. The project, which is scheduled to be completed by December 2011, will be conducted within the framework of CBI's NEWDIGS research programme in co-operation with the Agency and CIS.

Revisions to Chapter 7: Outsourced Activities of EU GMP Guide[17]

In view of the ICH Q10 guideline on the Pharmaceutical Quality System, Chapter 7 of the GMP Guide has been revised in order to provide updated guidance on outsourced GMP regulated activities beyond the current scope of contract manufacture and analysis operations. The title of the Chapter has been changed to reflect this.

European Medicine Agency's Committee for Advanced Therapies Adopts Five-Year Work Program to Foster Development of Advanced Therapies[18]

The European Medicines Agency's Committee for Advanced Therapies (CAT) has unveiled a Work Program to 2015, intended to help increase the number of advanced-therapy medicinal products (ATMPs) that make it from the early research stage to the market.

European Medicines Agency Widens Public Access to Documents[19]

The European Medicines Agency (EMA) has published its new policy on access to documents related to medicines for human and veterinary use. The new policy is part of the Agency's response to increasing public demand for more openness and transparency. It will give wider access than ever before to documents held by the Agency, while it ensures that personal data and commercial confidential information remain adequately protected.

Finland

Finland Issues New Regulation and Guideline for Labeling and Packaging Leaflets for Medicinal Products[20]

The regulation and guideline for labeling and packaging leaflets for medicinal products have been amended. Regulation 1/2010 and guideline 1/2010 of the Finnish Medicine's Agency come into force on 30 October 2010, thereby repealing regulation 5/2005 of the National Agency for Medicine and guideline 2/2005 of the National Agency for Medicine previously issued on the matter.

New Fimea.fi Web site Opened[21]

The new site is divided into sections dedicated for target groups: Public, Healthcare professionals, License holders, Veterinary medicines, and Medicines. Sections intended for all site visitors are About Us and Legislation.

Sweden

Swedish Medical Products Agency Evaluates Pilot Project of Joint Scientific Advice Meetings[22]

The pilot project of joint scientific advice meetings arranged by the Dental and Pharmaceutical Benefits Agency (TLV) and the Medical Products Agency (MPA), ended 30 June 2010. The project was evaluated by the MPA, the TLV and the companies involved during autumn 2010. It may still be possible to apply for joint scientific advice until a conclusion has been reached and published regarding the continuation of the project.

United Kingdom

MHRA Communication Strategy 2010-2015 Published[23]

This strategy builds on the solid foundations laid by the previous two communications strategies, but this time sets out the importance of careful prioritization and selection of activities, particularly in terms of what the Agency can help to deliver within the current and future funding constraints. This strategy recognizes the importance of continuing to maintain relationships built up over previous years. However, this time it identifies the public as the primary stakeholder on the basis that it is them to whom the Agency's business belongs, and on whose behalf they work and regulate. It is, however, recognized that the public makes for a large and diverse audience. Although the MHRA will continue to engage and communicate with as many public stakeholder groups as is practically possible, they also acknowledge they cannot do this all on their own. They have identified three additional priority stakeholder groups they hope will help to deliver their service to the public: healthcare professionals, industry and their own staff.

MHRA Conducts Informal Consultation as Part of the Project to Consolidate and Review UK Medicines Legislation[24]

The MHRA has published a second informal consultation with interested parties on opportunities it identified to reduce regulatory burdens as part of the

project to consolidate and review UK medicines legislation. Any responses to this informal consultation should have been submitted by 22 December 2010.

Asia/Pacific

Australia

Australian Regulatory Guidelines for GMP Clearance for Overseas Manufacturers[25]

The draft Australian Regulatory Guidelines for GMP Clearance for Overseas Manufacturers sets out revised requirements for obtaining and maintaining Good Manufacturing Practice (GMP) Clearances for overseas manufacturing steps for registered and listed medicines, including APIs (Active Pharmaceutical Ingredients) produced overseas. The main changes to the current guidance are as follows:

- clarification of assessment requirements and processes for getting GMP clearance for overseas manufacturing sites;
- the addition of a list of sponsor responsibilities in obtaining and maintaining those clearances;
- amended evidential requirements to address difficulties experienced by sponsors in obtaining particular documents from regulators and manufacturers (including delays in the release of inspection reports);
- a description of the criteria used for granting Clearance approval and determining its duration;
- the addition of TGA performance timeframes for the assessment of applications;
- new provisions describing the circumstances in which an application will be rejected or lapse; and
- the addition of procedures for the review of GMP clearance assessments.

The Therapeutic Goods Administration Has Commenced a Streamlined Submission Process for Selected Prescription Medicines Applications in Australia[26]

The Parliamentary Secretary for Health and Ageing, Catherine King, has announced a key milestone in reforming the regulation of prescription medicines in Australia. While maintaining the scientific rigour of TGA's evaluation process, efficiencies will be achieved by:

- early notification of the details of applications, three months in advance, to allow the TGA to undertake effective resource planning
- streamlined processes for evaluation of applications, with all requisite data provided at the time the application is lodged

Australia Establishes Risk-Based Approach to GMP Audit Frequency[27]

The Office of Manufacturing Quality is responsible for the ongoing assessment of manufacturers' compliance with Codes of Good Manufacturing Practice (GMP). On-site audits are conducted as the most direct method of assessing a manufacturer's compliance with GMP and form the cornerstone of regulatory programs worldwide. It is common for a manufacturer's product range, key staff, equipment, premises, procedures, financial status, etc., to change over time. As these have the potential to impact on GMP compliance, manufacturers are audited on a regular basis to verify continued compliance with manufacturing standards. The TGA has established a risk-based approach to guide the scheduling of audits based on the compliance history of the manufacturer, the products made and the manufacturing processes undertaken.

Australia Establishes Transparency Review of the TGA[28]

On 16 November, Parliamentary Secretary for Health and Ageing, Catherine King announced a comprehensive review of the way in which the Therapeutic Goods Administration (TGA) communicates its regulatory processes and decisions. The review will focus on improving the TGA's transparency.

The decision to establish the review reflects community concern about the lack of information made available by the TGA. The purpose of the project is to improve public knowledge of regulatory decision-making and to enhance public understanding of the benefits and risks of therapeutic goods so that the Australian community can understand how the TGA operates and the reasons for its key decisions.

China

Selection of New Members for the 10th Chinese Pharmacopoeia Commission Started[29]

The 2010 edition of Chinese Pharmacopoeia has come into effect as of 1 October 2010. The selection of new members for the 10th Chinese Pharmacopoeia Commission has started. Recently, the State Pharmacopoeia Commission released the Notice on Selection of New Members for the 10th Chinese Pharmacopoeia Commission on its official Web site. The selection of new members for the 10th Chinese Pharmacopoeia Commission marks the start of the compilation of the 2015 edition of Chinese Pharmacopoeia.

Japan

Japan's Pharmaceutical and Medical Devices Agency Publishes Its Annual Report FY 2009[30]

PMDA published its Annual Report for fiscal year 2009, detailing its activities, progress, and recommendations for improvement.

Singapore

Singapore's HSA Hosted 14th International Conference of Drug Regulatory Authorities (ICDRA) which Sees Record Attendance[31]

Through the four day program, 30 November to 3 December 2010, the 14th ICDRA aimed to provide opportunities for regulators to share and discuss current and topical issues of global concern. For example, access to quality medicines, counterfeit medicines, pharma-

covigilance, clinical trials and lessons learned from pandemic H1N1.

North/South America

Canada

Good Laboratory Practice (GLP) Recognition for Canadian Facilities: Reminder to Schedule Your Inspection before the End of the Transition Period[32]

On 30 April 2010, Health Canada released the finalized Guidance Document Non-Clinical Laboratory Study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice to guide sponsors who submit non-clinical study data on Canada's GLP requirements. All non-clinical studies (domestic or foreign), as defined in the Guidance document and initiated after 30 April 2010 are expected to comply with the GLP guidance document requirements. Canadian facilities generating GLP studies are expected to have been assessed by the Standards Council of Canada (SCC), the OECD recognized Canadian Monitoring Authority.

Designated by Health Canada as the Monitoring Authority for GLP compliance of Canadian test facilities, the SCC is a federal Crown corporation that promotes efficient and effective standardization in Canada. In addition to recognizing GLP compliance which sponsors can use to support a Canadian drug application for market authorization, SCC also operates various accreditation programs including one for testing and calibration laboratories. The abovementioned Guidance document provides for a one-year transition period in order to allow sufficient time for Canadian facilities to fully complete the GLP recognition process.

Health Canada and the SCC are reminding sponsors that Canadian facilities generating nonclinical study data in support of submissions or applications involving pharmaceutical, radiopharmaceutical or biologic drugs for human use, should have applied for GLP recognition and been found to be compliant with GLP by the SCC before 30 April 2011 which marks the end of the one-year transition period.

Health Canada Updates Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)[33]

Although no major changes were made to GUI-0027, the present edition of this document includes updates to terminology, clarification of existing requirements, and additional requirements such as annual product quality review.

Health Canada Publishes Annex 3 to the Current Edition of the Good Manufacturing Practices Guidelines – Schedule C Drugs (GUI-0026)[34]

The present edition of this document includes new interpretations added under the following sections: Personnel, Raw Material Testing, Quality Control Department, Finished Product Testing, Stability, and Sterile Products.

USA

Request for Comments on the Food and Drug Administration Fiscal Year 2011-2015 Strategic Priorities[35]

FDA posted its draft Strategic Priorities FY 2011-2015 to ensure that key stakeholders are given an opportunity to comment on this document. The purpose of this document is to outline FDA's strategic intentions and plans for the next five years (fiscal year (FY) 2011 through 2015). This document identifies four key cross-cutting strategic priorities and four strategic program goals that will guide efforts to achieve FDA's public health mission and to fulfill its role in supporting the larger mission and strategic goals of the Department of Health and Human Services. The four cross-cutting strategic priorities are: (1) Advance Regulatory Science and Innovation, (2) Strengthen the Safety and Integrity of the Global Supply Chain, (3) Strengthen Compliance and Enforcement Activities to Support Public Health, and (4) Expand Efforts to Meet the Needs of Special Populations. The four strategic program goals are: (1) Advance Food Safety and Nutrition, (2) Promote Public Health by Advancing the Safety and Effectiveness of Medical Products, (3) Establish an Effective Tobacco Regulation, Prevention, and Control Program, and (4) Manage for Organizational Excellence and Accountability. The document can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/StrategicActionPlan/UCM226907.pdf. Comments can be submitted to http://www.regulations.gov.

US FDA on Facebook and Flickr[36]

FDA published a page helping people connect with them on Facebook and Flickr. It can be found at http://www.fda.gov/NewsEvents/InteractiveMedia/ucm226596.htm.

FDA Issues Regulatory Science Report[37]

The U.S. Food and Drug Administration today unveiled a report outlining the agency's plans to advance regulatory science through its Regulatory Science Initiative. Regulatory science is the science of developing new tools, standards and approaches for assessing the safety, efficacy, quality and performance of FDA-regulated products.

The report, which can be found at http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm228131.htm, provides examples of current FDA activities in regulatory science and also considers how advancements in the field can help deliver better, safer, more innovative products to Americans in seven different public health areas.

US FDA awards $904,000 to Pan American Health Organization for information "hub"[38]

The U.S. Food and Drug Administration announced the award of a $904,000 cooperative agreement to the Pan American Health Organization (PAHO) to research and develop an information hub for medical products and related regulatory processes and systems in the Americas Region.

The award will help FDA, and all PAHO member states, to better understand other countries' regulatory systems, support capacity to use harmonized standards and guidelines across countries, and prevent, and if necessary

respond more quickly to, problems in the medical product supply chain. The "hub" will collect and produce data and map structures and processes in the areas of medical products, including drugs, biologics, vaccines, medical devices and other medical products, and related regulatory processes and systems.

US General Accounting Office Publishes: Biological Laboratories: Design and Implementation Considerations for Safety Reporting Systems[39]

As the number of biological labs increases, so too do the safety risks for lab workers. Data on these risks--collected through a safety reporting system (SRS) from reports of hazards, incidents, and accidents--can support safety efforts. However, no such system exists for all biological labs, and a limited system--managed by the Centers for Disease Control and Prevention (CDC) and the Animal and Plant Health Inspection Service (APHIS)--applies to only a subset of these labs. While a national SRS has been proposed, design and implementation are complex. In this context, GAO was asked to identify lessons from (1) the literature and (2) case studies; and to apply those lessons to (3) assess CDC and APHIS's theft, loss, or release (TLR) system for select agents, such as anthrax, and (4) suggest design and implementation considerations for a labwide SRS. To do its work, GAO analyzed SRS literature; conducted case studies of SRSs in aviation, commercial nuclear, and health care industries; and interviewed agency officials and biosafety specialists.

According to the literature, effective design and implementation of a safety reporting system (SRS) includes consideration of program goals and organizational culture to guide decisions in three key areas: (1) reporting and analysis, (2) reporter protection and incentives, and (3) feedback mechanisms. Program goals are best identified through stakeholder involvement and organizational culture, through assessment. Case studies of SRSs in three industries--aviation, commercial nuclear, and health care--indicate that (1) assessment, dedicated resources, and management focus are needed to understand and improve safety culture; (2) broad reporting thresholds, experience-driven classification schemes, and local-level processing are useful SRS features in industries new to safety reporting; (3) strong legal protections and incentives encourage reporting and prevent potential confidentiality breaches; and (4) a central, industry-level unit facilitates lesson sharing and evaluation. While the CDC and APHIS Select Agent Program (SAP) has taken steps in the three key areas to improve the usefulness of the TLR system for select agents, steps for improvement remain. Specifically, the agencies have taken steps to better define reportable events, ensure the confidentiality of reports, and dedicate resources to use TLR data for safety improvement. However, lessons from the literature and case studies suggest additional steps in the three key areas to enhance the usefulness of the system. For example, lowering reporting thresholds could provide precursor data and limited immunity could increase the incentive to report. Finally, the CDC and APHIS are in a unique position--as recognized authorities in the lab community and with access to TLR reports from across the industry--to guide SRS evaluation and ensure safety lessons are broadly disseminated. For a national safety reporting system for all biological labs, existing information--about labs' organizational culture and the lab community's limited experience with SRSs--suggests the following features in the three key areas: (1) Reporting and analysis. Reporting should be voluntary; available to all workers; cover hazards, incidents, and less serious accidents; accessible in various modes (Web and postal); and with formats that allow workers to report events in their own words to either an internal or external SRS system. (2) Reporter protections and incentives. Strong confidentiality protections, data deidentification processes, and other reporting incentives are needed to foster trust in reporting. (3) Feedback mechanisms. SRS data should be used at both the local and industry levels for safety improvement. An industry-level entity is needed to disseminate SRS data and to support evaluation. GAO recommends that, in developing legislation for a national SRS for biological labs, Congress consider provisions for certain system features. GAO also recommends three improvements to the CDC and APHIS TLR system. HHS disagreed with the first two recommendations and partially agreed with the third. USDA agreed with the three recommendations.

US GAO: FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress Is Needed[40]

FDA increased the number of foreign drug inspections it conducted from fiscal year 2007 to 2009, but still conducts relatively fewer foreign drug inspections each year than it conducts domestically. In fiscal year 2009, FDA conducted 424 foreign inspections, compared to 333 and 324 inspections conducted in fiscal years 2007 and 2008, respectively. Using a list FDA developed to prioritize foreign establishments for inspection, GAO estimated that FDA inspected 11 percent of foreign establishments on this list in fiscal year 2009. At this rate, GAO estimated it would take FDA about 9 years to inspect all establishments on this list once. In contrast, in that same year, FDA conducted 1,015 domestic inspections, inspecting approximately 40 percent of domestic establishments. GAO estimated that at this rate FDA inspects domestic establishments approximately once every 2.5 years. Further, FDA's approach in selecting establishments for inspection is inconsistent with GAO's 2008 recommendation that FDA inspect, at a comparable frequency, those establishments that are identified as having the greatest public health risk potential if they experience a manufacturing defect, regardless of whether they are a foreign or domestic establishment. Instead, its foreign inspections continue to be driven by the establishments listed on an application for a new drug, instead of those already producing drugs for the U.S. market.

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The New and Improved Pre-Approval Inspections Program

By Rochelle Runas, ISPE Technical Writer

The Regulatory Town Hall Forum held 8 November 2010 at the 2010 ISPE Annual Meeting in Orlando, Florida, USA focused on current and emerging issues related to Pre-Approval Inspections.

US FDA Pre-Approval Inspections (PAIs) may be conducted before the Agency approves a new drug to be marketed in the US. These inspections occur following FDA's receipt of an NDA or ANDA and focus on the manufacture of a specific drug. PAIs are designed to verify the accuracy and authenticity of the data contained in these applications to determine that the establishment is following commitments made in the application. PAIs also assess whether the establishment can manufacture the product in the application in conformance with GMPs.

Overview – FDA's PAI Program Revisions and Trends

Tara Gooen, Team Leader, Office of Compliance, FDA/CDER/DMPQ, gave an overview of revisions and trends in the FDA's PAI Compliance Program to align the program with the "Desired State" as part of the FDA's Pharmaceutical Quality for the 21st Century initiative. Specifically, in May 2010, the FDA carried out its first major revision of its PAI Compliance Program since the early nineties, laying out a number of inspection scenarios based on risk, the application filing, site, and reflecting ICH Q8 (R2), Q9 and Q10 principles. The FDA also covers small and large molecules for the first time.

Gooen reviewed related revisions to the FDA Pre-Approval Inspections Compliance Program Guidance Manual (CPGM) – essentially the SOPs used by investigators which provides valuable insight into what investigators will be looking at during an inspection. The revisions reflect enhanced internal collaboration among FDA staff, including the implementation of a Knowledge Transfer Program to produce product and process knowledge from CDER to the ORA for inspection preparation for high risk/complex products and processes; international collaboration; integration of a BLA pre-license/approval inspection program (most of the program is handled within CDER); and samples are collected for-cause only.

The following criteria may be grounds for a priority inspection:

1. Establishment is named in an application to the FDA for the first time, including establishments that have never been inspected or have been inspected only for non-application drugs

2. First application filed by an applicant (for coverage of finished dosage manufacturing and testing)

3. First ANDA filed for an approved drug (for coverage of finished dosage manufacturing and testing)

4. Finished product contains a New Molecular Entity (NME) (does not apply to supplements)

5. Finished product content assay has a narrow range (e.g., 95 to 105% labeled strength for narrow therapeutic index drugs) or drug is expected to require titrated dosing (does not apply to supplements)

6. Finished product or API is manufactured by a substantially different manufacturing process or dosage form than previously covered at the establishment

7. API derivation is high risk (e.g., API is derived from animal tissues) or the intended use has significantly changed (e.g., API previously used in non-sterile product is now intended for a sterile drug product)

8. Numerous application submissions or certain site/process/product changes that are expected to pose significant challenge to the state of control of the facility or process

9. Profile class status of application product or API is "unacceptable" or not updated via a site inspection within the past two years (three years for control laboratories and four years for packaging and labeling), for original applications or significant pre-approval CMC supplements

Inspectional coverage is focused on an evaluation of three areas:

1. Readiness for Commercial Manufacturing (consisting of five parts: investigations/trends, material handling, contamination, procedures, process feasibility)

2. Conformance to Application

3. Data Integrity – A Data Integrity Audit with the possibility of FDA action against companies that commit data fraud or provide false information to the agency.

For further details on the three areas above, see below section, "Investigator's Perspective of the New PAI Compliance Program."

Gooen said the major reasons for a PAI withhold recommendation between 2003 and 2009 were:

- Pending enforcement action/previous deviations persist
- Firm not ready/drug not made here/facility withdrawn
- Insufficient development data/production/process controls
- Inadequate lab controls
- Inadequate QA functions

Investigator's Perspective of the New PAI Compliance Program

Ernie Bizjak, FDA Investigator (Drug Specialist), Baltimore District/Northern Virginia Resident Post, further explained the three objectives of an inspectional coverage as was mentioned in Gooen's presentation (see above section, "Overview – FDA's PAI Program Revisions and Trends"):

1. Readiness for Commercial Manufacturing
2. Conformance to Application
3. Data Integrity Audit

"These objectives are the meat and guts for the investigator," said Bizjak. "It's what we're going to be looking at when we're out in the field."

Readiness for Commercial Manufacturing

The goal of Objective 1, Readiness for Commercial Manufacturing, is to determine whether the establishment has a quality system designed to achieve sufficient control over the facility and commercial manufacturing operations. It is broken up into five parts:

1. Objective 1A – Assessment of manufacturing and laboratory investigations related to the proposed commercial process, as well as any corresponding change control reports. This would include:
   - OOS stability test results for biobatch
   - Analytical method changes due to problems found during validation
   - Significant deviation involving similarly manufactured marketed drug product

2. Objective 1B – Sound and appropriate sampling and testing program for components (including APIs), container/closure systems, in-process materials, and finished products. For example:
   - Justification for statistically based acceptance criteria
   - Are samples representative?
   - Are critical steps evaluated?
   - Adequacy of Supplier Qualification

3. Objective 1C – Sufficient facility and equipment controls to prevent cross-contamination. For example:
   - Evaluation of the HVAC system in an existing facility that is bringing in a product with a highly potent API.
   - Introduction of a beta-lactam antibiotic to a large pharmaceutical manufacturing campus.
   - Cleaning validation for multi-use equipment.

4. Objective 1D – Adequate procedures for controlling changes, investigating failures/deviations, complaints/adverse events, conducting recalls, and reporting this information to FDA. These topics fall under Quality Systems, which could be evaluated by an examination of how the firm handles already marketed product (Drug Process Inspections Compliance Program). "Typically with a Pre-Approval Inspection you're conducting a general GMP audit as well," said Bizjak. "It's nice that we're tying things together."

5. Objective 1E – Evaluate the feasibility of the proposed commercial process and manufacturing batch record, which would include instructions, processing parameters, and process control measures. "This basically answers the question: How well does the firm know their manufacturing process?" said Bizjak. This would include:
   - Review of scale-up batch(es)
   - Studies to establish the range of processing parameters
   - Process Validation activities, if completed

Conformance to Application

The goal of Objective 2, Conformance to Application, is to verify that the formulation, manufacturing or processing methods, and analytical methods are consistent with information contained in the CMC section of the application for the biobatch, proposed commercial batch, and API. This would include:

- Observing processing and/or testing operations
- Compare the biobatch manufacturing process against the proposed commercial batch record

Bizjak emphasized that as an inspector, observing processing and/or testing operations is the most important part of this area and that inspectors are inclined to go out onto the floor and see what operators are doing rather than sitting in a conference room reviewing SOPs.

The Knowledge Transfer Program facilitates this area well, according to Bizjak, because field is now receiving input from reviewers and SMEs at the CDER Office of Compliance, which allows field to do more thorough inspections, especially when complex manufacturing techniques and processes are involved.

Data Integrity Audit

The goal of Objective 3, Data Integrity Audit, is to audit hardcopy and/or electronic raw data to authenticate the data submitted in the CMC section of the application. For example:

- Laboratory notebooks and associated chromatograms generated during release testing of biobatch
- Failure to include aberrant test results in CMC section
- Improper invalidation of OOS results

Concludes on next page.

Reviewers on Inspection – An ONDQA Perspective

Christine Moore, Deputy Office Director for Science and Policy, Office of New Drug Quality Assessment (ONDQA), which evaluates NDAs, INDs, and sNDAs, said the frequency of reviewers participating in inspections has recently increased.

Moore said reviewers on inspections are "not a new thing" and reviewers have always had an opportunity to participate in inspections. Traditionally few NDA PAIs have had reviewer participation. That is now changing due to more complex regulatory approaches with a push toward Quality by Design (QbD), an increased emphasis on shared knowledge and expertise with other offices, and working in a more integrated fashion with respect to review, compliance, and inspection. "One of the big lessons of QbD is that we all need to work together," said Moore. "That's not only on the industry side; that's on the agency side as well."

Recent ONDQA inspection participation activity increased from five reviewer inspectional trips in 2007 to 16 in 2010 (figures include PAIs for NDAs and sNDAs, and pre-operational reviews and for-cause inspections).

Sending reviewers on inspection adds value to both the reviewer and the inspectional team, said Moore. The reviewer gains an increased understanding of the process and product, which can help resolve certain review issues related to the application. It helps reviewers to understand scale-up and process control rationale, in particular for QbD-type applications with more advanced control strategies, including implementation of on-line monitoring systems and related models. Reviewers on inspection are valuable to the inspectional team because the reviewer provides specific areas of expertise and intimate knowledge of the application. Overall, the reviewers' participation promotes collaboration and exchange of ideas based on expertise, which can facilitate a more productive inspection.

With the traditional approach to review and inspection, information flow from the ONDQA reviewer to the compliance officer to the investigator was linear with little overlap. The integrated approach CDER is working toward, first explored during the ONDQA CMC Pilot Program in 2005, pulls all these groups together for a more seamless and open information flow.

With respect to QbD applications, reviewers suggest to industry the following considerations for a PAI:

- Knowledge management is key to QbD success
- Tracking and trending of product quality and process is important
- It is extremely useful to include science and technical personnel participation, including those responsible for:
  - Lab scale development
  - Design space development
  - PAT
  - Manufacturing
- Quality System should be capable and prepared to handle demands of QbD, PAT, and/or Real Time Release Testing (RTRT) approaches

Investigator's Perspective of the New PAI Compliance Program

Continued.

Case Studies

Bizjak provided case studies from PAIs he conducted or participated in, with the last study being a positive experience:

Case Study 1

There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications.

Specifically, laboratory investigation % and manufacturing investigation ! were opened on 8/31/09 and 9/8/09, respectively, in response to content uniformity results that did not meet the Stage 2 acceptance criteria (AV) for X Tablets, batch A. No assignable cause was determined, no preventative action was taken, and batch A was rejected. There was no evidence that additional investigation was conducted prior to manufacturing batch B which followed the same manufacturing batch record. Batch B met specification and was submitted to the agency to support application Y.

Case Study 2

Specifically, the current master batch record for X Sustained Release Tablets does not specify any in-process hold times, even though control of processing time was identified as one of the processing parameters in the process validation protocol. Processing time is critical for controlling moisture.

Case Study 3

Situation: Pre-approval inspection for site transfer of ophthalmic drops. Firm had to build a new sterile filling suite.
What I Observed: Firm developed a Project Validation Plan which had a description of the main processes and systems, list of validation activities, and reference to the corresponding documents. "This made it easy for me to go through and find the documents that I wanted to review," Bizjak said. They also performed a risk assessment on the compounding and filling processes to identify Critical Quality Attributes (CQAs), assess the criticality and risks associated with the identified CQAs and determine the residual risks associated with the CQAs and corresponding controls that should be evaluated during validation. "They were able to share the risk assessment and I was able to quickly see how well they understood the manufacturing process," said Bizjak.

An Industry Perspective on a Joint Inspection

Frank Hallinan, Senior Director of Quality, Pfizer, USA, gave an overview of the company's experience as the pilot project for a joint FDA/EMA Pre-Approval Inspection (PAI) conducted in April 2009 at Pfizer's Grange Castle facility in Ireland.

The "Joint Inspections" initiative was part of a recent project triggered by the Transatlantic Economic Council (TEC) in which Europe and the US agreed to collaborate in the execution of inspections of pharmaceutical sites globally with the goal of administrative simplification.

The week-long PAI of the Grange Castle site for a parenteral freeze dried antibiotic product in a vial involved two Irish Medicines Board (IMB) Inspectors and two FDA investigators. Each agency issued separate reports of observations, with the FDA providing a FDA 483 at the close of the inspection and the IMB presenting verbal observations at the close of inspection, followed by a written report a few weeks later.

Overall, Pfizer found no fundamental differences between a traditional IMB and joint inspection or between inspectors. From the company's perspective, the inspection was similar in content and inspection styles were observed to be closely aligned, particularly in the context of some key subject areas, including aseptic practices.

However, there was more spontaneity with respect to requests for documentation and to tour and/or observe certain operations, which proved challenging at points given IMB and FDA teams were divided into four concurrent work streams. There also were more requests for raw data contrary to historical inspections.

Nonetheless, it was worth the effort, said Hallinan. "It was an overall successful experience for the site that was extremely positive and valuable. It was an opportunity for site personnel to present and interact with two major authorities at the same time, which was a unique experience. It also was an opportunity to develop confidence at a young site and improve procedures and regulatory compliance via simultaneous dual agency perspective. There was good engagement within and between agencies and between agencies and the site team. It was efficient and Grange Castle was approved as a manufacturing facility in both regions."

Hallinan said Pfizer was motivated to participate in the inspection for several reasons, including there being an opportunity to potentially save time and negate duplication of effort in the future. "For Grange in 2009 we had 11 inspections by boards of health, approximately 1 per month," said Hallinan. "There were benefits associated with having this two for the price of one."

International regulatory authorities are obliged by law to have systems in place to verify GMP status of product manufacturers with the most common way of accomplishing this through routine GMP inspections. Different approaches are used for manufacturers outside of their national territory, e.g., reliance on results of inspections performed by other countries supported by Mutual Recognition Agreements, Memoranda of Understanding, and PIC/S (which US was not a part of until recently). Those approaches are often limited in scope and subject to restrictions.

As a result, a pilot project on international collaboration for GMP inspections for APIs, extending beyond EU and US regions, was announced July 2008 and has since been extended to include medicinal products, said Hallinan. Previously limited to PAI's, companies are now invited to participate in joint re-inspection (routine surveillance) where both the US FDA and EMA plan to inspect a facility in a similar timeframe (centrally authorized products). Further details can be found in the 23 September 2010 EMA/FDA Interim Report on the International API Inspection Pilot Program, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097431.pdf.

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ISPE ENGINEERING PHARMACEUTICAL INNOVATION

Q & A with FDA

The following are questions from the Regulatory Town Hall Forum audience and answers from Forum presenters Joseph Famulare (Senior Director, Genentech); Ernest Bizjak (FDA); Tara Gooen (FDA); Frank Hallinan (Senior Director, Genentech); and Christine Moore (FDA).

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Q (to Hallinan): If we added reviewers to the joint inspection you had, what would you think that would look like?

A (Hallinan): It would be beneficial at one level, but it would be a level of complexity that could pose problems and we need to think about it in advance and try and ensure that it is recognized that there is a certain number of people who can support the event, but there isn't an infinite number of people. Therefore we can manage four, five different simultaneous complex issues at the site, but we can't necessarily manage eight simultaneous issues.

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Q (to FDA): Regarding drug product PAIs, is there an expectation for the drug product validation batches to utilize API that comes from a validated process?

A (Gooen): Currently our expectation is that both the API manufacturing process and the drug product process must be validated prior to distribution of the drug product. I think it is in everyone's best interest to make sure you have a good quality API when going forward with your product development, process development, process validation, and the later stages of process validation.

A (Bizjak): The validation of the API supplier should be looked at as part of the supplier qualification as well.

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Q (to FDA): Instead of a EU inspector and FDA inspector, shouldn't there be a trend of having an international inspector?

A (Gooen): I definitely agree. I think we are moving in that direction and need to in order to utilize the global resources we have toward doing inspections. US has recently joined PIC/S. That will help towards more integrated and uniform training and the efforts of ICH to harmonize guidance and hopefully more in the future.

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Q (to FDA): Although you say you're going toward this mutual recognition, it seems like you're going more toward joint inspections. Having had joint inspections in my company between different agencies (from the US, MHRA, and Germany) with the Turkish Ministry of Health, I know that this is a difficult issue to handle for the pharmaceutical company. Now, the Turkish Ministry of Health is going toward not recognizing European and FDA approvals, so if we want to import from Europe or the US, the Ministry now requires self audits in those countries. I am afraid that things are not going toward mutual recognition but more toward splitting. Is there any aim to work together with emerging countries so that everyone can benefit from these mutual recognitions? Otherwise it would be difficult to import goods from one country to another.

A (Famulare): Mutual recognition is a path FDA took and did not end up with a successful completion of that goal with the EU. In my later days in FDA I think there was a path toward joint inspections that may eventually lead to shared inspections whether or not two inspectors came or whether one could share their report with another. So, the hope or uprising for mutual recognition by FDA I think is probably a distant chance. I think Turkey is in a unique situation, not having an MRA with the EU and US. Advocacy groups such as EFPIA are working vigorously to try to overcome some of those challenges so materials can flow in and out of Turkey and to allow that when there's not the possibility, for example, for Turkish inspectors to be able to broadly go out and inspect other countries due to resources or language differences, etc. Certainly that's been discussed. In one of the meetings with EFPIA there was an explanation given of the role of PIC/S that may bridge some of the gap between Turkey, Europe, and the US.

A (Gooen): There is still discussion internally of mutual recognition. The joint inspection program is being seen as part of the education process so that we can all learn about the different systems. I don't think the vision has been dropped, it (joint inspections, shadowing on inspections) is another step in the process.

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Q (to FDA): What is the procedure for requesting pre-operational reviews?

A (Gooen): There is what we call a Field Management Directive that relates to pre-operational visits. It's a procedure for companies to request a pre-inspection, if you will, (e.g., "We're doing something new and want to run it by you."). You can contact your local district office and they'll get in touch

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Q & A with FDA

Continued.

with the Office of Compliance, with the Review division, and it brings everybody together to discuss any new and innovative approaches that companies would like to bring up. Also, in the PAT Guidance, if there are any PAT approaches you'd like to discuss with the Agency, you can contact the general address in the program and we can have those discussions with you as well.

A (Moore): To elaborate on that, we can have discussions either through a formal meeting at our location or through the procedures discussed by Tara and a visit at your site so we can see the facility and equipment in place.

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Q (to Gooen): In regards to data integrity and fraud, are you talking about fraud that is negligence (person makes a statement as true, that they're not sure is true) or willful intent to deceive (person makes a statement as true, when they know that it is not true)?

A (Gooen): I'm talking about both situations. The main purpose of the data integrity audit is to ask the question, the CMC section reviewers are looking at, is that an accurate representation of what happened and is that representative information. The program talks about both contextual and factual integrity. Factual integrity is, for example: Is the I not dotted, is the T not crossed, or was there something we forgot to put in there? Contextual integrity is, for example: A specific laboratory sample was run three times, it failed twice, and one time it passed and the passing information is what was submitted in the application. The application integrity policy is a significant program in that if the policy is invoked it stops the review of any applications in house and any that come in from the company. The threshold for the application integrity policy does not include intent, rather is based on a statement of material fact. Is what was presented not representative in a way where it impacts the outcome of the review?

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Q (to FDA): Does the PAI inspector typically read any parts of the marketing application prior to an inspection?

A (Bizjak): Yes. From my own experience, we now have access to databases where the electronic submissions are being stored by the reviewers and we are looking at some of those details in the CMC section particularly before going on an inspection.

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Q (to FDA): Will inspectors start consistently expecting to see CQAs and CPPs identified in applications and reviewed during PAI?

A (Moore): There has been, I believe, for a long time an expectation that CPPs are defined in the application. If you look at ICH Q8 (R2), it talks about both the QbD or enhanced approach and also a minimal approach. In the minimal approach, what's presented in ICH Q8 (R2), it talks about how an application should define CQAs, CPPs, as well as QTPPs. That's one thing we're seeing regularly in the applications on the small molecule side … From the inspectorate side, what I hear is that is one of the first questions asked is, what are your critical processes and critical process parameters.

A (Gooen): Yes, investigators ask for this information on inspection. That's primarily how PAIs start. Explain your process, what's important in your process, and explain what your finished product specifications are. Investigators may not always have the most updated terminology (CQAs, CPPs, etc.) and use those particular acronyms. We start with: Tell me what's important? … That's the basic point.

A (Bizjak): Firms have said every parameter is critical. That doesn't provide a lot of confidence to me that they really know what they're talking about.

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Q (to FDA): Are US plants inspected more than plants outside US by FDA?

A (Gooen): Yes, at this point. There have been published GAO audits on this. One reason is because the statute requires domestic inspections to be conducted every two years and there isn't the same requirement for foreign inspections. However, there has been a major shift in resources within the Agency, within CDER and ORA, to counter this effect. I can't say we're exactly there yet, but there is movement to do many more foreign inspections and we have almost doubled the number of foreign inspections in the last two or three years, so we are shifting resources appropriately based on what we're seeing globally. It's tough due to finite resources. Inspections are expensive.

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Q (to FDA): Is there any plan to do any kind of joint inspections or mutual recognition inspections in India and China?

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Q & A with FDA

Continued.

A (Gooen): Yes, a lot of the people based in India and China do inspections, but their primary function at this time is on education and communication with the local regulatory authorities and in the future they plan to do more in-house in-country inspections. But there's no expectation that the India office will handle all of the inspections that need to be conducted in India, it's just a portion of the work plan.

A (Famulare): TGA, FDA, and EMA agreed to do joint inspections and shared inspections of APIs as a starting point in third countries. That was heavily engaged in India and China (see 23 September 2010 EMA/FDA Interim Report on the International API Inspection Pilot Program, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097431.pdf) …that beginning effort started around 2007, 2008 coming out of the Transatlantic Economic Council (TEC) dialogue… the second part is formalizing the program more for PAIs as for the facility Frank had presented.

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Q (to FDA): Is the Japanese health authority part of this program to date?

A (Famulare): Currently, no, because it's really been worked out of this Transatlantic Economic Council (TEC) dialogue between US and EU.

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Q (to FDA): Does the data integrity portion of the PAI include development data? If so, what is the scope relative to GMP data, such as conformance lot data, and how much do you audit process development data?

A (Gooen): The data integrity portion of the inspection is really related to what's filed in the application and in the last several years OPS has been requesting additional pharmaceutical development information. So, if that's provided in the application there's a real chance that that could be a part of the data integrity audit. The development data is necessary for evaluating process feasibility. The development data is the scientific data that supports your proposed commercial manufacturing process. We audit process development data in that respect, to make sure there's scientific justification behind what you plan to do.

A (Bizjak): As an example, before going to a foreign inspection a reviewer asked me to follow up on some development data they had concerns about. That's probably the most typical initiation for looking at that type of raw data.

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Q (Famulare): When you say you require adequate process development data, you're not referring (particularly pertaining to small molecules) to process validation data?

A (Gooen): We don't need to see all the studies that demonstrate that the product is ready to be distributed based on the manufacturing process at commercial scale. But process validation also includes pharmaceutical development data, the process development, and any justification that goes into supporting the proposed commercial scale manufacturing; that is something investigators will look at on a PAI.

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Q (to FDA): Do investigators view change management and change control as the same thing?

A (Gooen): I think that is semantics. To us it's the same type of system. I know change management is typically the terminology that's being used in ICH documents, whereas change control is typically a term you'll hear on inspection. It's really synonymous.

Q (to FDA): When I look at the ASTM E2500 approach, change management would be an engineering/GEP function versus change control, which would be managed by a quality assurance group.

A (Gooen): From an investigator compliance perspective, we're thinking top down, what's changing in your manufacturing process or changes that you want to make in your equipment. Any change needs to be appropriately evaluated and handled under the quality system's change management system.

A (Susan Schebler, PQLI Session Presenter, from the audience): The lifecycle approach is what is significant here because they overlap significantly in the manufacturing part of the lifecycle. But, if you're in the development part of the lifecycle, they're very different. When you're talking about the ASTM 2500 it's going to apply differently to different parts of the lifecycle. But if you compare the two definitions, change management includes more, it's the whole system, it's how it fits in with the other quality systems. Change control, if you look at the WHO and EU definitions, it's about maintaining a validated state. So, significant overlap, but some subtle differences.

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Q & A with FDA

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Q (to FDA): Can an adverse finding (bad deviation) on an inspection be so bad that even though it was thoroughly investigated and remediated, can it still cause you to withhold recommendation?

A (Gooen): Generally the statute requires that we approve an application unless we have a reason to withhold. The only reason why I would see we would maintain that withhold recommendation is if we still have overall cGMP concerns about the ability of the site to manufacture under cGMPs moving forward. But if there was a finding in the laboratory, and it didn't affect marketed product, and it was thoroughly investigated, and you understand what happened, and moving forward that same problem has been corrected in your systems, we wouldn't maintain the withhold recommendation because there would be no reason to.

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For further information, the following sites are available:

- FDA Pre-Approval Inspections Compliance Program Guidance Manual (CPGM):

  http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm071871.pdf

- Division of Manufacturing and Product Quality: cGMP Subject Contacts as of 12 May 2010:

  http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm096102.htm

- Questions and Answers on Current Good Manufacturing Practices (cGMP) for Drugs:

  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124740.htm PE

Q (to FDA): One of the things we think about with the different activity that's going on in our global economic environment, as companies make business decisions, what kind of discussions are the FDA having on evaluating risk to certain business decisions, (ex. when companies may be breaking off divisions, when you're taking away some of that R&D technology and data, losing some of that information and that process understanding when you break divisions off or send products to other countries). What are the risks FDA considers as those activities occur.

A (Moore): We recognize that companies make decisions and approaches based upon their economic needs and drivers; however we have to evaluate our products and processes against quality standards. We can't sacrifice quality standards.

A (Gooen): Going out on inspection, we're still going to ask for the scientific justification behind the particular change that you make, behind the particular part of the manufacturing process. I think that's where industry is headed - it's really important to look at knowledge management and how that information is captured and maintained in house. It's important to have that information when you need to make changes based on issues you're seeing in your process. In terms of the risk factors, the Agency does see change in management as a risk factor as well. There have been several studies where it says that when the quality managers have changed, six months down the road problems start manifesting that they wouldn't have seen otherwise. So that's another risk factor to think about.

A (Famulare): I think you hit on a major problem that not everyone's going to have the answer to. When you buy a molecule, do you buy the people, the process, the equipment, the building, the knowledge, or do you just buy the batch record?

A (Gooen): We had a recent case where the applicant was new to a particular type of manufacturing process but the contract manufacturer was not new. When the applicant says, here is the batch record that you need to use because this is what was filed. Then problems start happening. The contract manufacturer knows what's going on but they're not able to make those changes. That product has been approved but they have not been able to distribute for years because of what's going on back and forth. So, having that knowledge and that science is really important. When they went to scale up their process, it just didn't work. PE

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Business Process Management (BPM) Based Pharmaceutical Quality Management Systems: A Win-Win Between Compliance and Competitiveness

This article shows how a BPM-based Quality Management System optimizes the way to comply with today's evolving regulations and standards, while being even more competitive in the marketplace.

by François Versini

While quality in healthcare has always been a priority, recent guidance, namely ICH Q8, Q9, and Q10, indicates a new direction for organizing the system that enforces and guarantees the quality. Many working groups in many countries have chosen this topic and are trying to establish an appropriate approach for this new direction. The purpose of this article is to explain the new concepts, demonstrate how such a system may be implemented, and present the potential opportunities of adopting this approach.

Quality and Quality Management Systems under Scrutiny

In regard to product quality, problems such as stability or formulation are outlined on authorities' Web sites[1]; other articles question the quality of generics; others state that some fundamentals of quality management can be and should be enhanced, including traceability and data sharing throughout the supply chain and with the authorities.

In regard to global processes for quality assurance (company governance policies; corrective and preventive actions process, annual product review, clinical, or vigilance, etc.) there is information coming out that discusses new stringent expectations from authorities moving from end product control to process understanding.

At the same time and to support these products and product-related processes, attention is given to the information systems and the associated working methods to be deployed, including electronic documentation systems for the procedures, events and actions tracking and management systems, information systems validation, etc.

And last, but not least, there is new international guidance (such as ICH) available meant to improve the quality system organization. These guidances, however, have generated a wide range of misunderstanding, comments, and advice from the different parties involved. This article provides three reasons why this is the case.

1. Individuals are not talking about the same topic. They are not using the same definitions or philosophies. Therefore, the first thing that needs to be done is to define the different layers of the Quality concept.
2. Individuals are not looking at the topic from the same angle, which gives them different perspectives of what is possible and desirable. Some of the concepts may be handled by other departments, instead of the Quality function. Therefore, it is important to define the Quality Systems essentials and what departments need to be involved. It is important for all individuals to understand that different functions need to work together to make this happen.
3. Individuals with no experience with this type of process can find it difficult to imagine what process-based documentation can look like. Therefore, instead of describing theoretical cases, this article will present figures inspired by real examples.

The following discussion will demonstrate a specific way to structure a Quality System in

the pharmaceutical industry, integrating the three following logics:

- **Logic of Compliance:** ensuring all requirements and priorities for health and patient safety are considered and to answer what the inspection systems are waiting for.
- **Logic of Competitiveness:** at the opposite of what is usually thought, compliance and performance are usually connected in a positive way. When compliance requests make a big investment necessary, it is the same rule for everyone, which means that it does not generate a competitive disadvantage to anyone. Also, Compliance gives the right to enter a market, thus creates value, and is always profitable in the long run. In addition, an improvement in the manufacturing process, for example, often brings an improvement both in terms of profit and in product consistency and quality control.
- **Logic of Capitalization of Competencies, Knowledge Management, Business Process Modeling, and Management:** a system is to be thought of as a systemic topic, built with a systematic approach, ensuring that what is done is solid and will be the basis for future steps, combining all of the company's dimensions.

People often oppose those dimensions, thinking that an effort in one of them will jeopardize the other.

"I don't have the time to think about optimizing that domain. I am not concerned by these topics, which are not being inspected. I need to focus on the certification in XX months." "We should develop a workgroup to optimize that domain, and we'll pass the chosen solutions through the quality department and regulatory affairs in the end to ask them if what we set up is acceptable." "Let us begin with this first step. We'll think about the rest later, we have no time to document it all..."

It is such a pity to function in compartmented departments, in compartmented objectives, whereas having everyone on board would result in better ideas for all departments and all objectives. Maybe a workgroup for optimization will find a way to achieve conformity through a simple process; maybe the quality person, if participating in the group, will say that the operational people have an exaggerated idea of the constraints and that a win-win solution for both inspectability and operations is possible; maybe being courageous enough to build a structured documentation will save a lot of time when preparing for inspections and give opportunities to optimize.

Experiences in industries like the automotive sector or the food industry show how much it pays off to follow that road. Seneca[2] stated: "It is not because things are difficult that we do not dare; it is because we do not dare that they are difficult."[2] The key is in the synergy. We must stop thinking these are efforts in addition to what we already do. These are efforts that replace other efforts that we had planned, and that allow us to eliminate far bigger efforts that we would have had to do. Do we prefer simple projects that generate complicated processes or projects that deal with complexity in order to generate simple processes?

Compliance, Competitiveness, Competencies... a Challenge and a Potentially Dramatic Winning or Losing Strategy

What is Quality in the Pharmaceutical Industry and Elsewhere?

The purpose of the Quality System in the healthcare sector is to maximize health and patient safety. An important objective is inspectability and auditability. Authorities have the power to decide whether the pharmaceutical company may continue its activity or not. Nevertheless, the inspection mustn't become the purpose as such; it is an objective and a tool, connected to the purpose, which is health and safety.

The best way to manage quality: *Plan, Do, Check, Act*[5] and *say what you do, do what you say*.[9] The firm creates documentation that illustrates what is done and the inspection body will conduct a two-step verification process, including confirming whether the documentation is compliant with the regulations and whether the practice is in line with the documentation. Then the inspectors and auditors will identify gaps and areas for improvement.

This is a proven way to manage quality. It is important, however, that the tool doesn't overshadow the objective. The documentation is not produced solely for the inspector. It must be a good representation of the actual practice, a good tool to train qualified individuals, an opportunity to improve, and to ensure that activities are aligned with the purpose.

Quality Assurance in the pharmaceutical industry has been very advanced for more than 40 years, essentially driven by this very high objective, health and patient safety, very detailed regulatory guidance, a very structured inspection system, an obligation for qualified individuals to take responsibility, and some very rigorous regulated processes.

Those elements have been the lever for continuous improvement and high compliance. Compliance will reach a new level in each and every silo in the industry as interfaces and global governance continue to improve.

The industry has now reached a turning point, particularly with ICH Q10, giving guidance for the Pharmaceutical Quality System, and GAMP 5, reaching a new maturity level for the compliance and validation of computerized systems. The new route is defined and designed to combine the advantages and experience from inside and outside of our industry.

The history of quality is a long one in the industrial world, from the Ford and Taylor time, through Deming and Juran, to Toyota and Welsh.[3-8] The following will provide a summary of some major elements which have a large impact on the pharmaceutical industry now and in the foreseeable future.

Quality was not a major subject before the beginning of the 20th century, as there were fewer products than customers. Even low quality products could find a market. The first priority was productivity. Nevertheless several quality tools have appeared at that time, even if mainly aimed at productivity, such as statistics and a form of process improvement. Ford[3] and Taylor[4] are the most well known examples.

Quality became a concern as soon as the quantity of manufactured products surpassed the number of potential customers. The first quality wave created quality laboratories

in the factories, which allowed workers to perform tests and sort products, thus minimizing the percentage of bad products reaching the customer. A second wave professionalized the "inspection type" control with an advanced way to use statistics and perform process control. The third wave built documented systems with instructions and procedures, allowing for audits and coordination. It ended up with building an assurance type of logic with prevention rather than correction, anticipation rather than reaction, e.g., auditing suppliers to verify, before selecting them, that they will be able to deliver the desired quality, and management reviews to plan and review what is important for quality, etc.

In fact, in the middle of the 20th century, quality evolved drastically, based on the principles imagined or re-worked by two American "gurus": Deming[5] and Juran[6]; when Japan became a very dangerous competitor, managers from Europe and the US went there to see how the Japanese companies had transformed themselves from very low quality suppliers to best-in-class companies.

They discovered that one major root cause of this revolution was the fact that they had listened to the lectures of Deming and Juran, and had put into practice their ideas, while western countries had put their books with much respect on their library shelves.

One dilemma raised by Juran[6] in his conferences was the following: companies without a quality lab need to create one, but companies with a very advanced quality lab should work on downsizing it. An inspection step positioned after production may become an obstacle for defects prevention and production operators accountability. Such ideas are not to be implemented the same way by highly regulated sectors and classic businesses; nevertheless prevention and operators accountability are major concepts. Directly linked to these ideas and the way Japanese firms had implemented it, a "fourth wave" put human beings back in focus, by stating the following: "…it is with the ideas and the dedication of every operator that quality can be built and training people on quality and problem solving tools will allow for continuous improvement."

By the end of the 20th century, the "Quality Management Systems" wave was aimed at:

- integrating all dimensions, e.g., Quality, Hygiene, Security and Environment (QHSE)
- improving the ways to design and develop products
- reducing the percentage of product defects to a very low number (Six Sigma)
- optimizing not only the product and the manufacturing process, but all processes of all departments, interfaces between all departments, and within the whole organization (e.g., Total Quality Management, Lean Six Sigma)

One main example of "Total Quality Management" success is Toyota[7], and more recently what General Electric[8] achieved thanks to the Six Sigma methodology. These evolutions took place parallel to the rise of "Business Process Management," which generalized to the company level the techniques that were used in quality at the shop floor or departments levels. BPM brought the necessary tools to get rid of the functional silos, and making it possible, in far more efficient ways, to pilot the processes and the performance of a company.

Parallel to this evolution, the way to document the system also has been improved and it has reached a very helpful and recognized model, with ISO 9000.[9] That major standard has been taken as a template for other disciplines, such as environment, safety, etc. which makes it simple now to create an integrated management system combining all purposes without creating burden of documentation.

Why is this history of Quality so important? In order to better evaluate the importance of a concept, listing the obvious advantages is sometimes less relevant than analyzing the consequences of it being done poorly or not done at all.

Quality is all about doing things right the first time. This means that the process must be built in a perfect manner before performing it, checked and evaluated during the execution and afterward, and lessons must be learned from the results and the way it has been reached to improve it for the future and to build knowledge and competitive advantage. This is nothing new, it is the famous and enlightening *Plan, Do, Check, Act* of Deming,[5] but it is like a popular song: we remember the tune so well that we tend to forget the sense of the words…

Quality Essentials

We will now consider the main issues at the product level, documentation level, and process and system level:

- **Product Quality:** this is the historical focus of the regulatory system in the pharmaceutical industry. It provided a very high level of requirements and achievements thanks to the hard work of pharmaceutical companies and the surveillance and inspection of the regulatory bodies.
- **Quality Documentation System:** the national regulatory codes and the "good practices" force pharmaceutical companies to describe how they answer the requirements in procedures and instructions, and to keep very well defined records on product and test data and on the traceability of compliance with the procedures.
- **Quality Management System and Processes:** all the processes and documentation set up to ensure the quality of the product and of the practices constitute a system. ICH Q8, 9, and 10 focus on creating a real Management Process, built on approaches, such as Business Process Management (BPM), Risk Management, etc., that combine all the historic strengths of the pharmaceutical industry with the enhancements of the concepts from other industries.

The following sections address the issues we typically face at these various levels.

Product

At the product level, lack of acceptable quality is expensive: out of specification products that go to the bin, work on deviation or re-qualification to save it. We all heard the question "Why

do we have no time to do the things right, but we have the time to re-do them when they have been done wrong?"

Benchmark companies succeeded in getting out of the vicious circle of correcting instead of anticipating and preventing waste. Low product quality costs a lot. In addition, product quality is essential, an entrance barrier into the market. A company that can't prove to the authorities that the product quality is ensured loses its right to manufacture and commercialize products.

Documentation

Why are our documentation systems often characterized by many long procedures and instructions with repetitions? Why are there often repetitions of the regulatory texts on one hand and description of equipment on the other hand and still the need for them to be completed by training and operational documents?

The answer largely lies in the way procedures are traditionally developed. When creating a new procedure – which can be for covering a new operation, closing an inspection gap, or coping with a new regulatory requirement, people may simply add one more procedure to directly fulfill the need. It may be regarded as too time consuming to analyze and simplify, and make an addition in a well-defined context.

This is a very short term view that ends up with a mixture of many long procedures and instructions that will require far more time for maintenance. Moreover, there is a high risk of inconsistency between all of these documents, which can end up causing other problems.

Furthermore, if we want to comply with an additional regulation in the future (for example, when we need to comply with the FDA in addition to the European GMPs or to produce a Medical Device in addition to drugs) it will be a huge task to determine which part is already as it should be and may be used, and which part is to be created.

Benchmark companies establish structured documentation that will comply with the expectations of inspection bodies and audit organizations, while minimizing the volume and the maintenance required, and optimizing the structure to make it useful and adaptable. Poor organization of the quality documentary system costs a lot in terms of duplication of effort for creating and maintaining documents, difficulty to prove compliance, and to adapt to new regulations and new strategies.

System and Process

At a process and system level, there are other problems that will be further discussed.

The first problem is that people have very different views of what a process is, what a system is, and what model to copy. Many process approaches still have a limited ambition: to use the process representations to replace long texts in procedures. While this is a very good idea to do so, this is neither BPM, nor building a Management System. Benchmark companies build ambitious BPM approaches to ensure that they will cover what is essential to the company, both from compliance and competitiveness standpoints, and will represent the reality. They then make an abstract of what is to be documented as a top to bottom quality system: first what is common to all and generic, then the specifics.

A Quality System not based on a process approach may be disconnected both from strategies and reality, and can turn into practices and documentations that aim at making inspectors happy rather than being useful and maximizing performance.

The False Problem: What are the Boundaries of the Quality Function? The Strategic Subject: What is to be Managed in a Systemic Way?

In different companies, the Quality Function can have a very different range of responsibilities. In the pharmaceutical industry, the first dilemma is how to connect the quality lab (which is an operational step within the integrated supply chain, after manufacturing and before warehousing) with the quality assurance part (which needs to be independent from manufacturing to organize and judge the quality of the whole chain).

Connecting them makes the person in charge at the same time the judge and the one being judged; on the other hand, it is comfortable because the people playing the two roles often have similar profiles. The decision must be made after balancing the pros and cons.

Moreover, Quality is often essentially seen as a manufacturing topic, whereas others think that the same principles and methods should be applied to development, commercial, as well as finance and HR. With the **Sarbanes-Oxley** law, we have the proof that the Quality management principles are to be applied in finance. There are now some pharmaceutical companies in which risk management becomes a combined quality, security/safety and finance/strategy approach, based on the corresponding international standards that are very similar; it becomes then a major management process serving the priorities of the executive commitee.

Finally, the question arises whether or not a "process approach" should be run by the quality function? Should Quality take the lead on security and environment because systems should be organized similarly? Should quality work on all improvements, even the main "comex" objectives?

Some companies have a Quality function focused on the product in manufacturing, others create a Director for Quality, Hygiene, Security, and Environment, staffed in addition to project managers to work on any type of improvements. Some companies create two functions: quality keeps on the old scenario, and the second is called "progress" or "Six Sigma" or performance.

This article doesn't suggest one approach over another, as it will depend on the history and the nature of the company. However, organizations must develop a structure to deal with at least four key elements:

- **Risk Management and Action Alignment:** how the main risks for the company are brought to the attention of the executive committee; how all people in the company position their strategic, tactical, and execution actions

aligned with the decisions that have been generated this way.

- **Process Piloting, Information Systems Urbanization, Master Data Management:** how the main topics and information in the company are managed in one leveraged place and shared openly and protected when necessary.
- **QHSE Coordination:** how to leverage, for these four topics, the steps of the process, which are common (management responsibility organization, documentation, training, reviews, etc.)
- **Performance Improvement, both Continuous and Breakthrough**

Each separate company culture will determine whether or not to call this Quality, but no matter what a company calls it, the Quality function needs to exist. The discussion below will focus on what must be leveraged and piloted from a central function, and the most efficient tool to use to accomplish this. For the purpose of this discussion, we are calling it Quality.

BPM based QMS

Figure 1 illustrates a Business Process Management-based Quality Management System, which is a combination of real examples from pharmaceutical companies that have implemented this new process. Since some of these companies adopted these approaches several years ago, we are able to evaluate the real life advantages gained.

Figure 1 shows an example Management System of a Pharmaceutical Company described as a BPM model. In order to clarify the representation and simplify the use of the modeling afterward, the model is structured as follows:

1. The middle is the main (critical) path (for example, produce product)
2. The top shows the processes that pilot the main path
3. The bottom shows support processes (for example, Information Technology)

Individual roles and departments may not be shown on the diagram since it is only aiming to describe the main flows. Thus the Financial Director, for example, may not be mentioned by name, but still plays a crucial role as both member of the Executive Committee and as head of the relevant support process.

The figure is not structured around departments, but on the activities that produce the main products, documents, and data. For example, Design and Develop doesn't mean the R&D department, but rather the process to transform an idea into a fully defined product, ready to be manufactured and commercialized. The process is the result of teamwork between Research, Development, Marketing, Regulatory Affairs, Quality, and some Industry and Logistics services that anticipate the downstream processes.

The figure should be used as a top level map with each domain being described in a lower level map. Each process is then described with a simple map which we will call an actigram, showing each element of inputs and outputs (product, document, information), constraints and objectives (requirements, goals, indicators) and resources and supports (roles, IT Applications, Material Resources). These are the objects that are the subject of the modeling and at the very heart of any Process project. All areas in the company must agree on the inventory list of these objects (what are the master data,

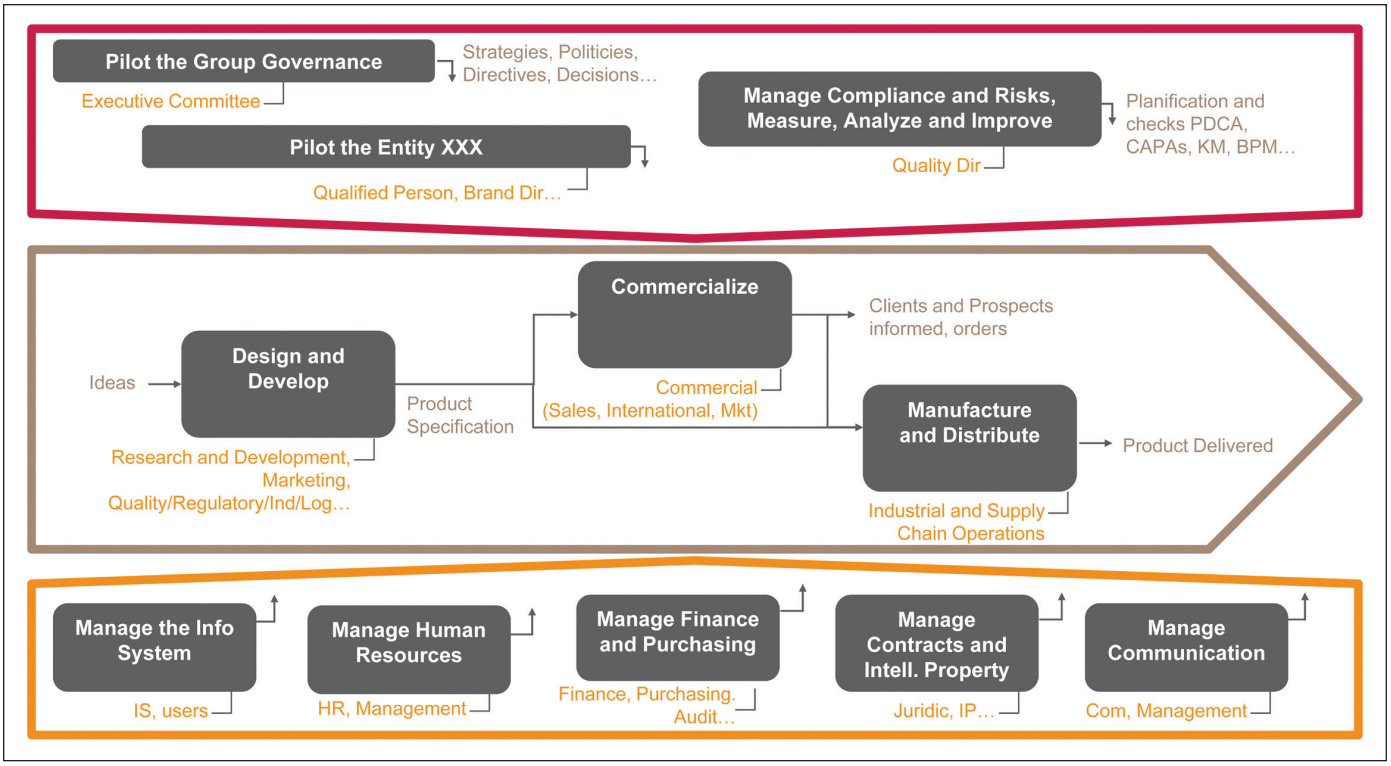

Figure 1. BPM model for the management system of a pharmaceutical company.

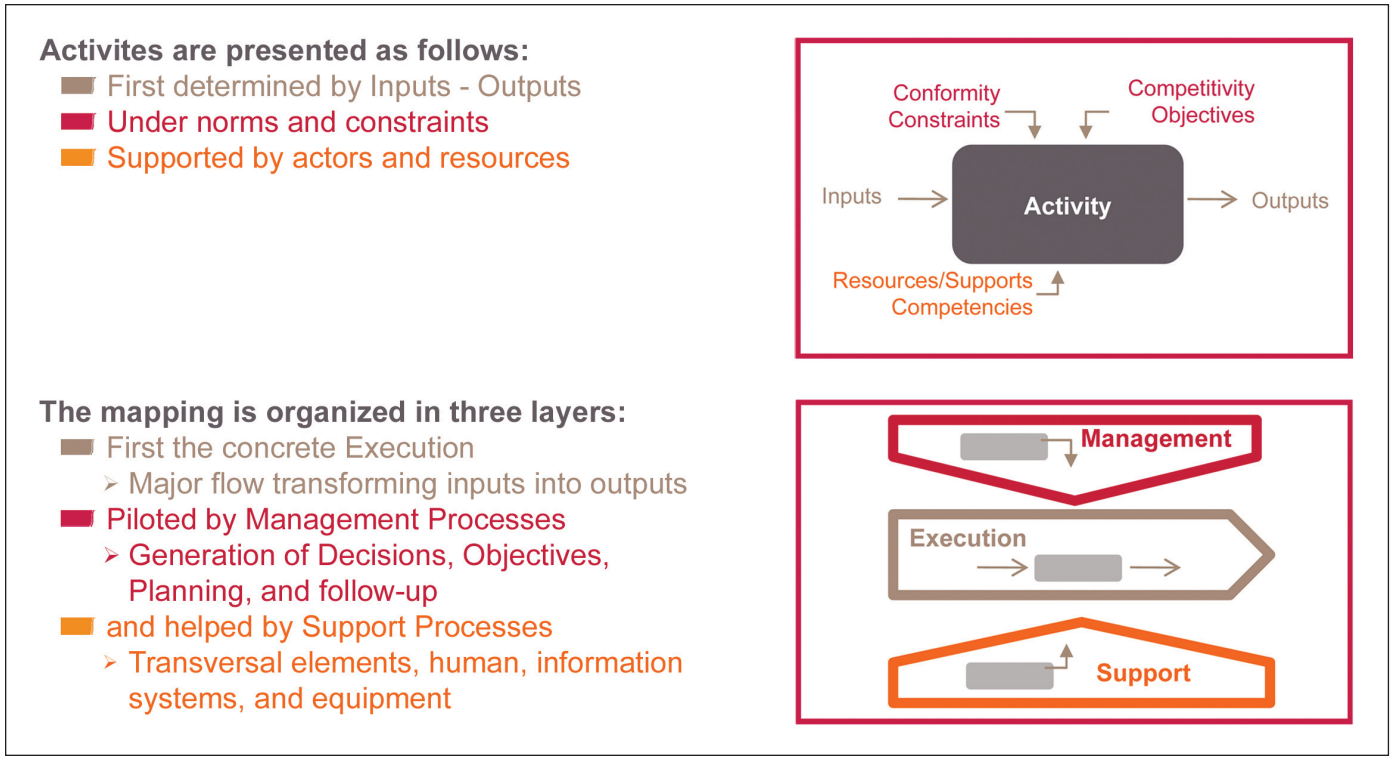

Figure 2. Representation and structuring rules: each activity in its environment, focusing on the what and the why.

main shared documents, the requirements, etc.) then in the representations that show the flows and the interrelations between those objects. Figure 2 summarizes the BPM principles.

Imagine the BPM project is advanced enough to cover its objectives for the company; how does it help with building an optimized Quality Management System? It is common practice to use the different levels of representation brought by BPM for the different levels of Quality Documentation, as shown in Figure 3:

- The general mapping and some actigrams may be imported in the Quality Manual.
- The appropriate logigrams may be imported inside the procedures and/or instructions.

It creates very efficient documentation. The Process representation aids navigation through the whole paperwork, allowing anyone – operator, manager, or auditor – to see the general picture then focus in on the appropriate area.

A major benefit is that the quality documentation is very close to reality, built with the real players, and focused on the essentials devoid of long sentences that may be interpreted several ways and focused on the main objects that are coherent throughout the whole company.

The project should adhere to the rule of modeling: first describe a generic model and then create versions of it to accommodate differences between some of the cases. Similar activities should be described by a unique model on which all involved people agree, and then create specifics for the differences between locations or departments, turning them into slightly different versions from that generic model. BPM is the way to make it possible.

Quality benefits in many ways from such an approach. Plants or Development can create documentation far more compliant, easier to understand, and easier to maintain. Many examples show a reduction by a factor of two or three in the number of pages, and an inspection in the end that was far more fluid and positive.

The combined pyramid of process maps and quality documentation allows far more efficient audits, internal or external, and therefore improvement, thanks to the readability. Also a given improvement can be duplicated in all areas where it should be since it is easy to identify all areas which perform the same generic activity.

Finally, the main benefit is the capacity to really manage the important processes to combine all regulation types together, in an efficient system that answers all requirements and leverage throughout the organization.

This quality system has a direct and major effect on product quality: it makes it simple for all employees to know how they should perform their tasks in order to be compliant; it optimizes the quality assurance processes like CAPAs, deviations, etc.; and it ensures that all processes are managed. Based on these key elements, good control is possible.

It is always difficult to measure the improvement obtained through such a re-organization. Volume reduction of procedures is often 50% and maintenance effort reduction is often several man-years for large facilities. This is usually, however, a combined result with an implementation of an electronic data management system or a re-organization.

It is easy to imagine the gain obtained by the non duplica-

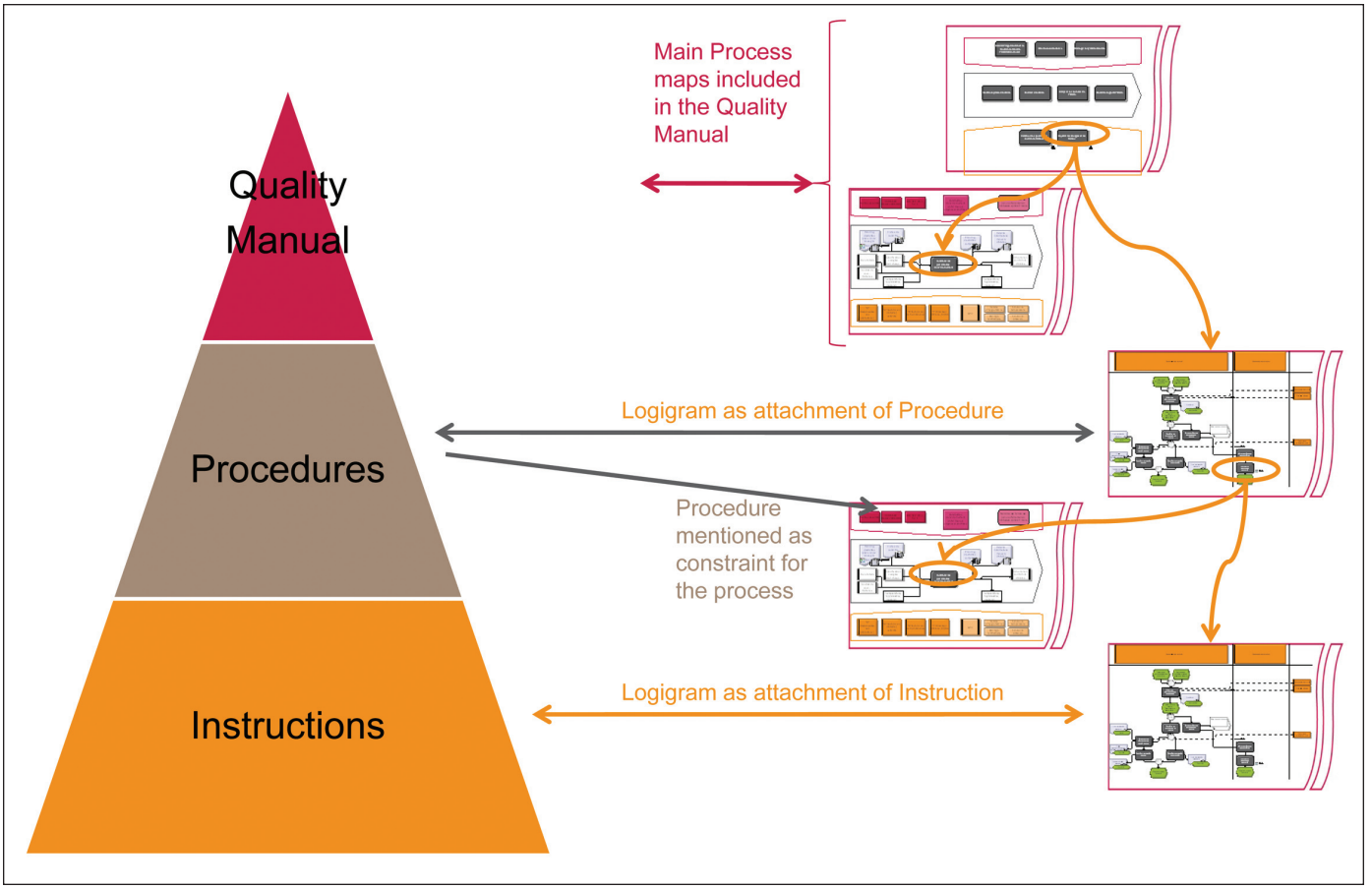

Figure 3. BPM and QMS: process maps show the why and the what, and structure the documentation detailed logograms describe the who, when, how.

tion: when a change is done somewhere, everybody benefits from it; and all consequences of non justified differences are eliminated. Such a system opens many synergies, and the gain for it will never be evaluated as such. It is becoming the normal way to organize quality in pharmaceuticals.

It is expected that having implemented ICH Q10 would be a criteria for reducing the frequency of inspections; it is not written, but this is the spirit, and it is very logical. When an inspector has verified a system according to ICH Q10 standards and then has inspected some details, he is far more comfortable about all the remaining perimeter than with a classical approach. Proof of its performance is given by positive inspections in areas where it was implemented and through the fact that the surrounding domains usually volunteer to implement an equivalent system. We shouldn't wait to get such benefits.

As a last example, Figure 4 shows how a map may at the same time be a logical extraction of the comprehensive representation of the management, execution, and support processes, and also position the chapters of the GMPs for a given plant. By extracting some of the lower level maps, it is easy and efficient to build a compliant documentary system.

What's Next?

Let us conclude with some perspectives. The ideas developed above should become natural within a short period of time, as ICH Q10 is being deployed. ICH Q10 is not, however, prescriptive on how to implement the principles. The given elements include ISO-type elements, such as creating a process mapping, management responsibility, and resource allocation.

As a result, there will be maps which will become tools for everyone. There will be some management processes which will be created and will change the way information goes up to the senior management and decisions are made on quality. There will be a new area of processes to be established for many pharmaceutical companies. The aim here is not to

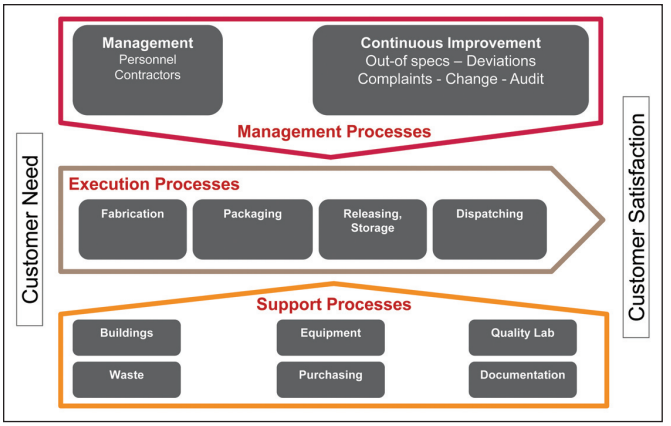

Figure 4. BPM model for a plant. Process mapping in relation with GMP classification.

explain what was written in ICH Q10, but to demonstrate the benefits for the pharmaceutical industry of implementing this new approach by illustrating some real life examples from other industries.

As a last image, I will discuss an example of a small plant, in which I was lucky enough to have my first job 22 years ago. The plant had been taken over by a large chemical company, which had brought over its own way to operate and manage. Among them, the "whole job concept," meaning that it was normal to:

- go beyond the boundaries of the job
- think in a lateral manner
- stimulate teamwork to identify the potential safety accidents and potential quality accidents
- ask all employees to be vigilant on what could have gone wrong and suggest ideas to prevent that it ever happens again

Quality and Performance Workshops were held, including two day-quality tools trainings for 100% of the people, one of the tools being the process concept (not yet the whole BPM logic, but already including the idea to describe the "as-is" and the "to-be" in a workshop in order to solve problems).

The people were conscious that there had been a "cultural revolution" in order to be able to adopt those ideas. Before that change, they had been afraid to let one know what mistakes they made, there were no such initiatives to improve processes together, etc. Today, they are still ahead on those ideas since that "cultural revolution." The process map they created seven years ago is one of the cleverest and most creative ones I've seen.

The result? They were small and they have been bought out several times. Each time, the buyer was planning to integrate the product of that plant in one of his big sites and then close the plant. Each time, after some months, the buyer was so astonished by the level of quality and the way people were working, that they never closed it and the plant is still there, standing as a reference.

They didn't know that their Quality focus and know-how would be the key to their survival, but so it was. They did it because it was the best way to ensure that the product be at its best, that everybody gives his/her best contribution and be proud of what he/she does, that a competitive advantage be built and kept. And it did make it possible. A systemic way for Quality makes all this possible: a win-win between compliance, competitiveness, and capitalization of competencies.

References

Figures included in the text are taken from the reference training and consulting material that i3L shares with its partners, Qameleon and ProductLife Group.

1. For example http://www.fda.gov/ for the USA, http://www.afssaps.fr/ for France, etc...
2. Epistulae morales ad Lucilium, Letters to Lucilium, Seneca, ca. 4 B.C.-65 A.D)
3. Henry Ford (1863 – 1947), founder of the Ford Motor Company, has been the sponsor of the mass production assembly line technique.
4. Frederick Winslow Taylor (1856 – 1915), an American mechanical engineer, is the father of scientific management, called after him "Taylorism."
5. William Edwards Deming (1900 – 1993) American statistician, professor, author, lecturer, and consultant. He made popular the concept of "Plan, Do, Check, Act," that he didn't invent, but taught in his lectures to the Nippon Keidanren, the Japanese managers organization, during the fifties. The idea is to first think and establish the objectives and processes necessary to deliver the expected results (Plan), then implement the new processes (Do), then measure and analyse the new processes, comparing the results against the expected results (Check), then make changes and improve (Act), and come back to a next cycle of Plan, Do, Check, Act and so on. There are various definitions of the four steps, other names for the steps, and equivalent cycles with more steps, but the main idea is in these few lines.
6. Joseph Moses Juran (1904 – 2008) management consultant. In his books and lectures, he built the foundations and the frame for the concepts of Quality Management.
7. Toyota raised the Total Quality Management concept to a form of perfection with the "Toyota way," including major ideas such as the "Lean Manufacturing" and Just In Time Production.
8. John Francis "Jack" Welch, Jr. (1935-…) CEO of General Electric between 1981 and 2001, took the opportunity of the "Six Sigma" method invented at Motorola's to develop his company, in all businesses types and all departments of the company.
9. The ISO 9000 family of standards represents an international consensus on good quality management practices. It consists of standards and guidelines relating to quality management systems and related supporting standards. The first versions of the standard were initially very successful, but gave to it a reputation of being heavy and bureaucratic. Many people summarized the philosophy of Quality Assurance and ISO 9000 by saying "say what you do, do what you say," meaning that the company needed to document clearly the activities that it had planned to perform and that it was really performing, so that an auditor could confirm that reality was in line with documentation, which was in line with the referential that the company wanted to comply with. The 2000 version changed drastically, incorporating ideas from BPM and EFQM : process based, focused on customer, performance and management. It is still very effective for the traditional Quality Assurance aims, but it adds very important dimensions, while allowing a far more simple, flexible and powerful format.
10. EFQM is a global non-profit foundation, which nurtures a network for innovative organizations and business leaders to share knowledge, experiences and good practice. EFQM is the custodian of the EFQM Excellence Model, which is

seen by many experts as the best management model ever thought. Companies that follow an EFQM approach are evaluated according to the best practices on 5 'Enablers criteria' (Leadership, Strategy, People, Partnership & Resources, Processes) and 4 'Results Criteria' (Customer, People, Society and Key Results). The modification between ISO 9000-1994 and ISO 9000-2000 is a convergence with some key ideas of EFQM, even if the two remain different: EFQM is an evaluation and benchmarking dynamic, while ISO 9000 is a standard against which to be audited and certified. EFQM meant "European Fondation for Quality Management," but is now a name that shouldn't be translated anymore.

About the Author

François Versini became Quality Director for a midsize pharmaceutical Group 10 years after having endorsed that same function for a global business unit of an American chemical multinational company. In between, he also held positions in Logistics, Human Resources, and Production. He founded i3L, a consulting firm which provides support to health and life sciences key players in conducting change management in terms of organization, quality, logistics, HR, and processes. i3L is an associated member of Product Life Group and this article has benefitted from several discussions with Dr. Erick Gaussens, Chief Scientific Officer of Product Life Group. He can be contacted by email: fversini@integration3L.com.

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Achieving a Validated Facility from a Set of Critical Quality Attributes

by Magnus Jahnsson, Firas Al-Saffar, and Anna Kälvemark

This article presents a risk-based work flow for design and validation of facilities, turning a set of Critical Quality Attributes into a validated facility. The main objectives are to improve quality assurance and traceability while saving cost and time.

Introduction

When the FDA presented the draft "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach"[1] in August 2002 the industry started looking for ways to translate this into a new, more efficient way of working. In the field of design and validation, many companies turned to two ISPE Guidance Documents: Baseline Guide on Comissioning and Qualification[2] and to GAMP 4[3] which both came out in 2001. They provided a framework for risk assessment with a lot of potential. Using this approach, systems were classified as Direct Impact (DI), Indirect Impact (II) or No Impact (NI). In the DI (and II systems in some companies), the components were in turn divided into critical or non-critical components where the critical components in the DI systems would undergo qualification while the remainder would be verified through commissioning. The general assumption was that this would cut time and cost in the burdensome validation projects.

One of the major problems with this approach was to actually make use of the result received during the risk assessment. How would this be converted into something valuable economically as well as for quality?

A practical challenge was to actually reduce the amount of testing or at least the amount of tests performed in documents controlled by a rigorous number of reviews, signatures, and approval.

This turned out to be the hardest thing to accomplish.

What would the tests within direct impact systems, but on non critical components actually look like? What about deviation handling? Exactly how many approvals were needed and by whom?

We experienced that the industry was somewhat reluctant to let go of control for the non critical components and functions within direct impact systems, even though letting go of them should not mean loosing control of final product quality. Thereby the cost and time saving effects of the risk assessment were to a large extent counteracted.

Managing the services of sub-suppliers, including their documentation, provided yet another challenge. To get full leverage, they must be equally mature and follow the same approach; separating protocols and testing to make use of the risk assessment. Testing is also often executed in parallel and applying two (or more) different test strategies at the same time would be counter productive.

Due to these challenges, the outcome was often that the execution of the validation in itself was cheaper, but the increased quality assurance needed through engineering and design to get there in an orderly fashion turned out to be as expensive for the whole project as the old all-encompassing validation method.

In late 2005, the ICH released the two well-known guidelines: Q8 – Pharmaceutical Development[4] and Q9 – Quality Risk Management,[5] providing a definition for two central concepts – Critical Quality Attributes (CQA) and Critical Process Parameters (CPP) as well as stating a preferred work flow for Quality Risk Management.

Even though the ICH Q8 – and the subsequent and current revision Q8(R2)[6] – is a document aiming for a very specific chapter in the Common Technical Document (CTD) table of contents and primarily relates to pharmaceutical development, the results and the philosophy of this guide is a foundation for further engineering, design, and the validation.

The ICH Q9 gives important guidance on where risk management is applicable and it very explicitly points at engineering and validation. This has given an indisputable mandate to work risk-based in the validation process. However,

the Quality Risk Management process described by the ICH Q9 is much more than just risk assessment and especially the risk control part is essential to ensure traceable and logical decisions on criticality. This is what GMP inspectors will expect to see when reviewing the qualification protocols.

Since then, ASTM has released the E2500 "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment"[7] and the FDA has released the draft guidance on process validation.[8]

Both the ASTM-standard and the FDA-guidance have so far had more of an impact in North America than in Europe and the rest of the world. But they address the concept of design and validation in very much the same way, arguing for quality by design rather than relying on the traditional validation at the end. The ASTM E2500 is the document that goes the furthest in outlining a practical, engineering oriented approach.

And it is evident that the creators of all four of these documents have been talking to each other as the nomenclature and the definitions are overlapping, creating a platform for a global common language in design and validation.

Looking at all four documents, combining and condensing the intentions, there are a number of important lessons that can be taken into a new work flow for the engineering, design, and qualification of facilities and equipment.

These are:

Critical Quality Attributes (CQAs): providing a much needed starting or reference point for the whole process. In most previous Impact assessments, the more generic term "Product Quality" was used. This was a much blunter tool, and using the CQAs will pinpoint what is really critical in a system in a better way. It is no longer enough to state that equipment in direct contact with the product is critical. Using the CQA as a reference point requires a rationale for why something in contact with the product makes it critical. One of the most probable reasons is to ensure that the CQA "sterility" is kept within the needed requirements. And the reason for the sterile requirements is of course to keep the product attribute Dose Uniformity within specifications during another product attribute, "the shelf life." Having to define the CQAs early therefore forces a better process understanding in the end-users organization and helps the engineers and designers to be right-first-time.

Critical Process Parameters (CPPs): are partners to the CQAs. They provide the sometimes multi dimensional design space within which the attribute meets the specifications.

Critical Aspects of Manufacturing Systems(CAMs): Talking of aspects rather than components gives a more accurate description of what is critical in a system or process. It could be components, material quality, alarms etc. It is also beneficial to distinguish between critical attributes which refer to the final product and critical aspects which as described above refer to criticality within the manufacturing systems. This is no official interpretation, but it provides clarity when discussing criticality.

Risk Control: The perception is that many companies did risk assessment, but not the risk control activities leading to the right level of verification for each aspect.

Verification: Although the word will not replace the words commissioning, qualification, or validation for the foreseeable future, it points the finger toward verification activities.

Find a new and better way. With all these new concepts, companies are looking for a new work flow for engineering, designing, and validating a facility in a risk and science-based manner that is: fast, cost-efficient, most importantly – securing quality and traceability, and ultimately, safe for the patient to use.

Methodology

After mapping the new work flow, it became obvious that the CQAs are the natural and necessary starting point for a new facility. The CQAs should be developed from the Product Attributes using science- and risk-based methods. That is not included in the scope of this article and should be part of the early stages of pharmaceutical research and development.

Finding and Agreeing on CQAS (Client and Supplier Agreement Needed)

Ideally this should be part of the Pharmaceutical R&D activities where the CQAs and the corresponding CPPs are identified, but in many cases, this has not been done, especially for products that are already on the market. Still the organization purchasing a new facility or line should know their product and process well enough to be able to provide the CQAs for the particular product and the production steps covered by the new investment. If this is not the case, the contract giver and taker(s) must develop these together. The driving force in this cooperation should be the organization that is actually going to perform the validation of the new facility or line. They are the ones benefitting from this approach initially. If the product owner is performing the validation, this will be an easy task as they also own the product specification. But in case the design and validation (or the entire manufacturing process) is outsourced as is often the case today, the coordination of the CQA-definition will be more of a challenge. In practice, the organization carrying out the validation has to have internal expertise that can translate the product attributes into draft CQAs. These then need to be approved by the manufacturer or ideally, the product owner if they are not the same.

The definition of critical systems is both a risk assessment exercise and system optimization. Previously the facility was designed, and then the design was divided into systems which in turn were assessed for criticality against a set of criteria. This is a bottom up exercise. Turning it around and defining the features and equipment necessary to meet the CQA-requirements enables a first verification that the systems chosen actually cover and satisfy all the CQAs. One example could

be sterilization where the choice between sterile or aseptic production, autoclave, or heat tunnel becomes transparent and easy to explain to an inspector. Another obvious advantage is that the high probability of a correct decision early in the chain is the foundation for cost and time control.

Defining CPPs for the Critical Systems in Order to Meet the CQAs

For new products – and for many existing products – the CPPs have been defined during the Pharmaceutical Development phase by the product owner. Then the work is already done and it is easy to move on to the next step. But if the critical process parameters have not been defined or are not universally known, as for example, the sterilizing cycle of an autoclave, now is the time to do it. The CPPs are the foundation for not only the OQ-testing, but also in part, the PQ.

As in the discussion about the CQAs in the preceding chapter, defining CPPs is easier for the product owner that can use an internal Development and Pilot Plant for this work. But if the design and validation or the entire manufacturing has been outsourced, it can still be done with the cooperation of the product owner and the equipment/system suppliers.

Each user requirement specification for a system should include the Critical Quality Attributes, which that particular system is satisfying. And each CQA should be connected to one or more CPPs that ensure that the attribute requirements have been met. Again, taking the example of an autoclave, the CQA Sterility is met by the CPPs Time, Pressure, and Temperature. The critical requirements in a system functional specification should ensure that the CPPs are within the specified range. A functional design review at this stage will ensure the link from the critical functions to the Critical Quality Attributes.

As mentioned before, when a supplier has to define the critical process parameter, it is advisable to include preferred equipment or system suppliers, who should be the real subject matter experts. By doing this they can, not only give valuable input, but are also prepared if they are to be part of the work flow, writing specifications and qualification documentation. And as was discussed in the background, there should be only one way of working throughout the project and to make full use of the suppliers, they also must align with the work methods used. This is one of the main challenges in a big project and why harmonization of the design and validation work is so important. If suppliers have to learn a new way of writing, testing, and documenting with every new customer they will be spending plenty of non-value adding time trying to adapt rather than the activities they should focus on, the functionality of their equipment, where they are the real subject matter experts. Figure 1 is a cut-out of a spreadsheet showing one way of merging Impact assessment with CQAs and CPPs in one document.

Define the Critical Aspects of Manufacturing Leading to CPP/CQA Compliance (Material, Components Alarms, etc.)

Now it is time to design the system in detail. When doing that, the different critical aspects of manufacturing systems also need to be identified. These are named aspects rather than components as they also could be material quality, surface finish, software functions, alarms, etc. Their common denominator is that they all ensure that a critical function or part of the system is designed to meet the functional requirements. As with the CPPs, it is preferable to involve the suppliers as much as possible for exactly the same reasons as above.

2 Product/System Impact Assessment

System		Product CQA					System CPP						
Name	CQA#	Bacterial Impurities	Solid Impurities				Temperature	Conductivity	Filter Pore Size				
WFI Still	1	X					X	X	X				
WFI Still	2		X						X				

Figure 1. An example of a CQAs and CPPs connected in a system impact assessment.

Make a Risk Analysis and Control Strategy for Each Aspect

So far the work carried out has been risk identification, and on a higher plane, risk assessment. Now it is time to make a more detailed assessment of the criticality for each aspect. The outcome of this is an elaborate control strategy for each aspect. This is where you determine whether a simple installation check is sufficient or if physical and functional verification is necessary. The key to this is that the proper subject matter experts[6] are involved in the activity.

The ICH Q9 does not define how scientific the risk control activity has to be. It can be done with using an FMEA or it can be done in a simple fashion as is shown in the cut-out from an actual spreadsheet in Figure 2, where the product risk and the detectability form the basis for the test strategy. It can even be done on experience as is stated in the PIC/S-guidance where it says that "Common sense and an understanding of pharmaceutical processing go a long way toward determining what aspects of an operation are critical."[9] The method chosen as shown in Figure 2 is based on a combination of examples from the ICH Q9 Briefing Pack,[10] where a number of different examples can be used as a starting point for risk analysis and test strategy. The final method must probably be tailor made to fit each organization that is carrying out the risk assessment but the examples are, in our opinion very practical and do not need much tweaking.

There is of course always the possibility that you find that it is not possible to control the risk of a specific aspect at this stage and then there is a need for re-design. Today this is something that is too often discovered during the validation phase, resulting in delays and cost increases. With the process described in this article, the risk for trouble shooting during validation should be minimized.

3 Risk Analysis of Critical Process Parameters

2.1.CPP: Temperature

CPP #1 Temperature	Requirements Spec. Doc. # XX00-T-000006		
Critical Aspects System Areas/Components	**Requirement Spec. Item #**	**Risk Scenario**	**Test Strategy**
Process	3.2.3, 3.3.2	The water does not fulfill the temperature requirement. Product Risk: High Detectability: High if sensors work	Measure temperature at each user point for at least five minutes. Challenge the lower temperature limit Etc.
Critical Sensors	5.3.2 (and 8.2.9.7), 3, 4, and 6	Water which does not fulfill the temperature requirement is used for process purposes. Product Risk: High Detectability: Low, no subsequent check points	Calibration certificates shall be delivered for all critical instruments. Calibration certificate for instruments used during calibration of instrument shall be current and traceable to a National Standard. Calibration reports for measuring devices (including recorder) of WFI Still shall be supplied. Sensor accuracy needs to be tested separately. Etc.

Figure 2. Critical aspects, risk scenario, and testing strategy.

Leading to a Validation Protocol

From each critical aspect of the manufacturing system, validation protocols for the system can now be created by matching each tag, alarm, etc. with an approved test strategy.

There is nothing new or revolutionary in the execution of the verification. The revolution is the chain of steps leading up to the actual verification. This chain should be clearly visible in the protocol. It must be possible to identify the paragraph in the specification that is tested in the protocol. When reading the protocol it should be possible to verify that the functional or design requirement was critical and why it was. The question why can then be traced back to the requirement specification that contains the CQA's and CPP's. Then the chain of rationales is complete and it becomes obvious why a test was critical and easy to explain this to an inspector. See the Purpose field in the validation protocol in Figure 3, which is detailed enough to ensure accurate traceability.

Another advantage with this approach is since the chain follows the traditional design chain where a high level requirement specification is broken down into a functional specification and then further and finally into a design specification. This allows for activities and reviews to be done in parallel by the same people, leading to synergy effects that the present risk-based validation practices seldom show.

Doc. Type:	Qualification Protocol	
Doc. Name:	XX00-T-000034 Qualification Protocol WFI Distribution, OQ Tests	Rev: 01

OQ Test: 1.1
Test:
Verification of the WFI loop temperature.
Purpose: To ensure that WFI loop meets the functional specifications required in XX00-T-000006, item 3.2.3, 3.3.2.
Method: • Connect a ....

Figure 3. Example of the connection between the OQ-protocol and the CAM.

The Complete Chain

As shown by the red line in Figure 4, below the chain needs all these activities to be complete but it is also obvious that there are many parallel chains emanating from the CQAs and it will require diligent quality assurance to ensure that all are traced throughout the lifetime of a project.

Results and Discussion

This work method is still very new to our business and it is not yet possible to put numbers on the time and cost savings. The experience so far can be summarized as follows:

The concept of CQAs is still very new to the pharmaceutical business, and as a supplier, it is not yet possible to rely on getting a well-founded set of CQAs from pharmaceutical R&D. Instead, the CQAs may have to be prepared together in the early conceptual study phase.

The advantage that has been obvious from the beginning is the increased transparency with regards to traceability. It is easy using the three documents shown in Figures 1-3 to follow and review the rationale for a qualification test directly to a Critical Quality Attribute. This has been a major challenge with previous work methods.

Another major advantage is that the scope of the qualification is defined much earlier in the process flow than with the older methods. This allows for much better predictability on cost and resource allocation during the different process steps. It also satisfies the concept of Right First Time.

Involvement of suppliers remains a challenge for two reasons. First, many suppliers do not only supply pharmaceutical equipment, services, or systems, but when they do supply to the pharmaceutical industry, most buyers do not require them to be part of the chain described above. And second, even if they are capable and interested in working in a risk-based manner, the many different approaches to risk-management from the buyers make it very difficult for them to find a way

of standardizing the delivery.

The workflow has, so far, been well accepted by engineers as it aligns well with the engineering and design process. The perceived amount of having to do things twice just because of risk management has been greatly reduced. However, the work process requires extensive internal training and alignment between all participating disciplines in order to keep a consistent level designing and validating all different types of critical systems in a larger project.

Conclusion

Since the emergence of risk-based design and validation in the early 21st century, the industry has sought after a cost-efficient, high quality way of carrying out this work. With the introduction of new regulatory guidance, the framework and the tools for succeeding are finally in place. The method described above is in compliance with the regulatory guidance, cost-efficient, and promises to be one way of delivering safety to the patients, while still using the resources and time available in the best possible way.

If the industry, both pharmaceutical manufacturers and suppliers, can agree in principal, on a safe and efficient way of designing and validating, more time can be spent optimizing processes and facilities rather than on non-value-added documentation and testing of non-critical parts of the processes. Again, to be able to leverage testing and documentation in an efficient way, suppliers must be part of the work flow, preferably from the definition of the process parameters. But this requires a very close cooperation between buyers and suppliers.

And finally, this workflow paves the way for fully computerized design and validation using modularized design solutions with predefined test strategies and verification protocols. In such a system, traceability is integrated by the relations in the design database. Especially the quality assurance activities around change control would decrease dramatically if traceability could be ensured within a database. Today, an enormous amount of time is spent ensuring that a change in design is captured in risk assessments, design reviews, traceability matrices, qualification protocols, etc., as it would be a

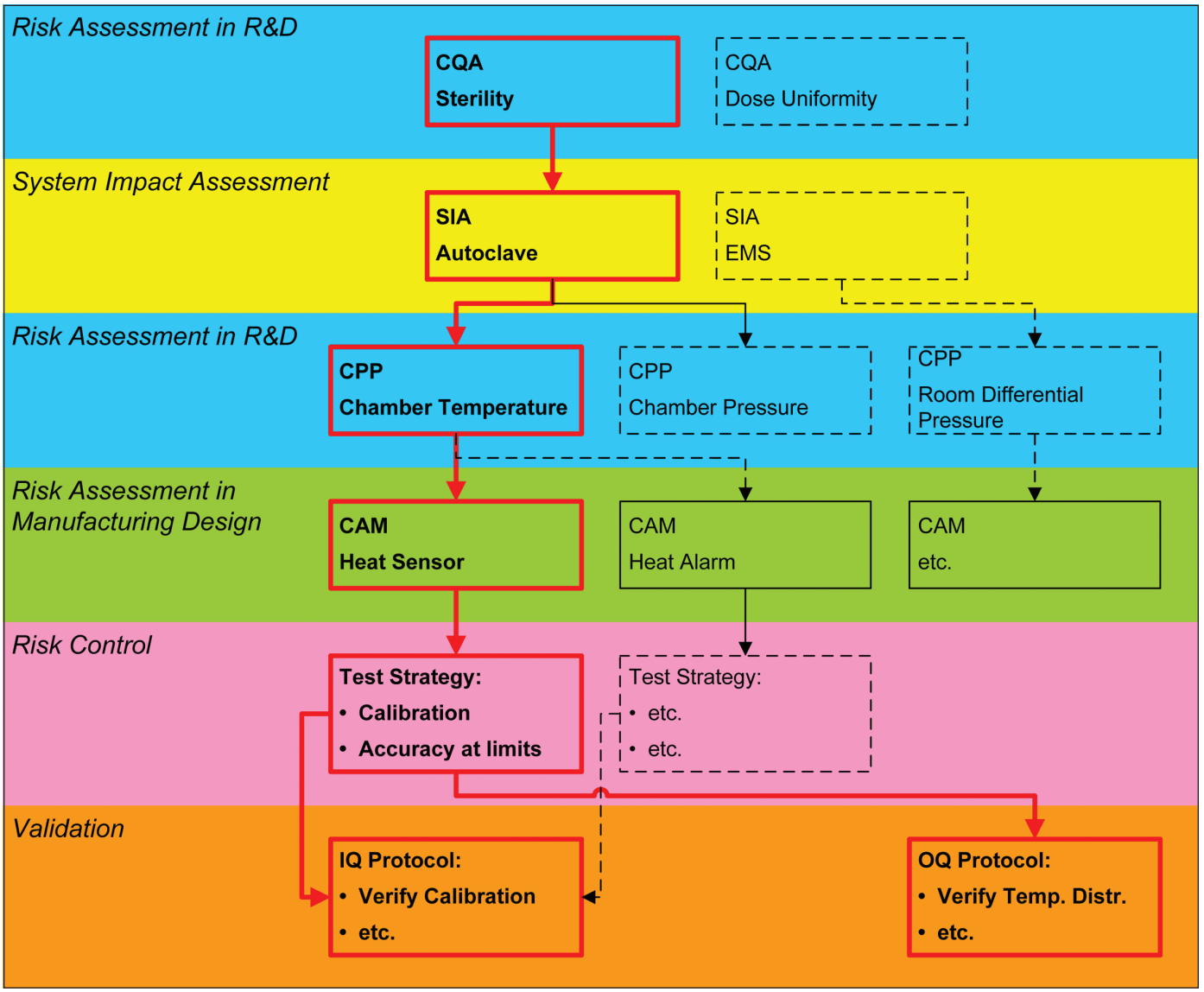

Figure 4. The process in a picture. The red line indicates one branch of liked activities.

disaster if an inspector found out that a validation protocol is referring to revision #3 in a specification when actually the final approved specification has revision # 5. Such a finding would effectively disqualify the entire quality assurance system. Being able to ensure, using relations in a database, that changes are considered in all the necessary subsequent activities, would truly reduce costs and increase quality in the process.

Glossary of Terms

Critical Quality Attribute (CQA): A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality [ICH Q8(R2)].

Critical Process Parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality [ICH Q8(R2)].

Critical Aspects of Manufacturing System (CAM): Critical aspects of manufacturing systems are typically functions, features, abilities, and performance or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety [ASTM E2500].

Risk Control: Actions implementing risk management decisions. Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk [ICH Q9].

Verification: A systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly [ASTM E2500].

Subject Matter Experts: individuals with specific expertise and responsibility in a particular area or field [ASTM E2500].

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Case Study: Application of the ISPE Baseline Guide for C&Q Yields Cost, Quality, and Budget Control

by Robert A. Young and Humberto Rosas

This case study provides an example of the positive results that can be obtained by the following principles set forth in the ISPE Baseline Guide® for Commissioning and Qualification, Volume 5.

Project Background

This article presents a case study on the positive results that can be obtained by following the principles set forth in the ISPE Baseline® Guide for Commissioning and Qualification, Volume 5.[1] This Guide when used appropriately is not only effective, but efficient for the commissioning and qualification of facilities.

The principles of this Guide were applied to the commissioning and qualification of a $45 million retrofit project for the manufacture of small molecule Active Pharmaceutical Ingredient (API). The project scope included the addition of a filter/dryer, a dispensing suite, a solids charging booth, and a purified water generation and distribution system. The retrofit portion of the project included rework of a dissolution tank, a reactor serving also as a still and crystallizer, a liquid charge booth, and the supporting utility systems. Overall, the project had 30 systems, half process related and half utilities.

After two challenging projects following the site acquisition in 2005, the site and the project team decided they wanted to improve delivery based on the lessons learned from these projects. One of the key decisions was to follow the corporate commissioning and qualification program that had been established based on the fundamentals outlined in the ISPE Baseline Guide. Using these fundamentals, the project and more specifically the C&Q work finished on time, under budget, and at a quality level received positively by the site.

This article presents key commissioning team activities related to these project phases: planning, design, document development, procurement and vendor management, construction, commissioning, and qualification.

Overview of ISPE Baseline Guide Approach

The purpose of the ISPE Baseline Guide Volume 5[1] was to define the baseline approach for C&Q of FDA regulated facilities, utilities, and equipment. At a summary level, the philosophy and approach promoted by the Guide was as follows:

1. Good Engineering Practices (GEP) as defined in the Guide make a significant contribution to meeting the regulatory demands of the pharmaceutical industry.
2. Qualification Practices are required where engineering systems may have a direct impact on product quality.
3. For systems that are not direct impact, GEP is satisfactory for testing and release of systems for use.
4. In order to complete any successful and streamlined qualification effort, a comprehensive plan should be developed which bridges the GEP/commissioning phases with the qualification phases of the project.

Planning (Strategy Development)

This was the third major project for the site after its acquisition five years earlier. Following acquisition, the first project brought a new product to the site. During this project, the site was converting to a new company culture and its practices. A second project immediately followed the first project to provide additional capacity. With a break in time between the second and third project, the site management and the corporate project delivery team had time to reflect and build on lessons learned from the prior two projects. This planning phase created a collaborative atmosphere which facilitated a

change in site culture about how large scale projects can be managed and supported. Three key learning points helped shape the C&Q approach for this project:

1. Process: the decision was made to follow the large-scale corporate C&Q facility delivery process as this model was successful on other projects. The changes from the prior projects will be highlighted in each section.
2. Resourcing: in alignment with the ISPE Guide on Project Teams (Section 4.4) and Roles and Responsibilities (Section 5.6), the following two key positions were staffed with company resources to address organizational gaps:
   a. A dedicated project sponsor at a management level was added to facilitate project decisions and assure adequate site support for the project. In the prior projects, sponsorship was part of an existing site role and support fell to a lower priority when production issues arose. This lower priority resulted in significant gaps in support and coverage of critical activities in the C&Q process including document reviews and issue resolution.
   b. A dedicated C&Q manager at a corporate level was added to guide the contracted C&Q firm, the project, and the site with the implementation of the large project C&Q delivery model. In the prior projects, support was provided through periodic visits to the site. Multiple leaders were then added at the end of the projects to drive closure to various outstanding C&Q activities. Continuity and consistency to the program principles were lost in the process.
3. Build on what had worked well in the prior two projects: for example, the commissioning concept (Section 5 of the ISPE Guide) of functional testing prior to qualification had proven to be highly valuable to the site in preventing problems in qualification.

A strategy document capturing the agreed upon changes from the lessons learned was developed and approved. However, this strategy document really came to life in the project, when site management ensured that their staff participated within the spirit of the strategy.

Learning Points:

1. Front end loading with appropriate resources provided time to reflect and produce needed changes and alignment around the C&Q approach.
2. A formal-approved strategy document captured and helped ensure understanding and agreement on the approach.

Design

The design phase set the stage for the integration of C&Q activities with project delivery. This phase progressed with very little change from previous projects except for the design review. User requirements, system boundaries, and system classifications followed the Baseline Guide principles.

Design Review:

- In contrast to the prior two projects, the concepts of GEP and enhanced design review presented in the Baseline Guide were leveraged to pull forward the work-load associated with verifying materials of construction for existing equipment. The design review involved testing the design against the user requirements. A key part of the structured design review as described in the ISPE Guide (Section 7.5.2) is to verify the acceptability of the product, raw material, and utility contacting materials in the new and used equipment and piping. To do this, the C&Q team worked with the process experts to develop a list of acceptable and expected materials of construction. Using the list, the new and existing component specifications and drawings were checked to verify the compatibility of the design.
- This simplified the IQ to verifying that the product contact materials were per design. In contrast to this, the previous projects did not include this level of design review for the existing equipment and instead more of a field exploratory approach was used during IQ. The approach had been to identify the materials of construction during the IQ and then write a statement of acceptability for each "as-found" material in the existing system. This was time consuming and required a large amount of documentation during the critical path phase of the IQ. Further, this moved the risk of finding an error in the decision to use existing equipment to the final qualification steps. In contrast to this, the enhanced design review established the acceptability of the expected materials early in the design phase and during the IQ only those materials found not to match the expected result required additional investigation.

Learning Points:

Leveraging the Baseline Guide concept of the enhanced design review to include existing equipment greatly simplified the IQ and removed work from the critical path during execution.

Document Development

The ISPE Guide (Sections 6 and 8) provides suggestions on ways to streamline protocol development. In the prior projects, document development and execution was given limited focus with regard to streamlining and reducing errors in protocols. Protocols of more than 500 pages in length had been produced making size a significant barrier to efficient review and error reduction. For this project, a key strategy was to minimize the cost of document development and make the best use of reviewers' and approvers' time by reducing the size of and minimizing errors in documents. Several methods were used to implement this strategy, including:

- The use of templates and pre-approved forms. This allowed the reduction of protocols to a much more manageable size between 50 to 100 pages.
- Data base management of component information for population of lists and automated form generation. Components included instruments and equipment.
- Peer reviews

The ultimate goal was to create documents that were right

Phase	Objective	Measures/Expectations
Draft Documents	Right First Time	• Author: no issues on format, replication, template, etc. • SME reviewer role: no content or technical criteria gaps
Routing for Review and Approval	Timely and Efficient Review	• Two week review and approval • One review and one approval cycle • After one week review, new comments go to next revision

Table A. Document development, review, and approval accountabilities.

the first time. For forms, this meant no form generation errors when populating component data. For protocols, this meant one review and one approval cycle.

In the prior projects, document generation quality was raised as a concern. Document reviews were lengthy with multiple review cycles before all the comments could be incorporated for document approval. In contrast for this project, specific strategies were put forth to eliminate document errors and clearly define accountabilities for generation, review, and approval of protocols and packages.

Table A provides a high level overview of the process. The process began with the C&Q team's responsibility to create error free documents. Part of producing error free documents was a peer review at an administrative level. The purpose of this review was to eliminate document generation errors, such as formatting, typographical/spelling errors, date errors, replication errors, and errors in the table of contents, so that reviewers and approvers could focus on technical content.

Another key part of the document development strategy was to get support from the reviewers for a single review and approval cycle. In the past projects, documents tended to get incomplete reviews. This led to many cycles of review as new issues were found with each review. As a result, documents could face delays of several weeks in the review and approval process. In contrast to this, a formal and full document review with returned comments was expected in one review cycle. The comments were addressed and the document was then routed for approval. Any new comments after the initial review would be considered for the next document revision. The logic for the next revision approach was that the individual would have been able to sign at initial review if the issues had not been present. The success of this strategy was demonstrated in the reviews. A very limited number of comments were received and shorter than expected review times were experienced on most documents. Typically, documents completed the review and approval process in a week without an effort to expedite.

While the document review expectations in Table A were shared with and agreed to by the lead team from the beginning of the project, the key difference in changing behavior from prior projects occurred through the support of the project sponsor. The project sponsor's active involvement kept the visibility of issues related to timely document review high which strongly encouraged site management and in-turn their staff to meet their commitments to the lead team.

Learning Points:

1. The use of proven document templates and forms minimized document development time and errors.
2. Taking the time to manage information on components and keep it accurate eliminated data errors from the very beginning of document development.
3. Good document generation quality was not a given. Formal processes and checks minimized document generation errors.
4. One review and approval cycle worked when initial document quality was high and expectations were fully understood and supported by the team.

Procurement and Vendor Management

The project had a number of procurement channels which evolved over the course of the project - *Figure 1*. The challenge was to ensure that data and documentation requirements supporting commissioning, qualification, and system maintenance were clearly communicated along with the design requirements. Unlike the prior two projects, the project resourced key C&Q positions early which allowed the creation of a data and documentation specification. In alignment with the ISPE Guide (Section 4.2 and 4.3), this specification followed the good engineering practices of stating the documentation required for ongoing operation and maintenance, and the documentation required to demonstrate compliance with applicable regulations and codes. This specification was issued with the request for proposal to the vendors.

The data and documentation requirements were specified by component type and at a package level for vendor packaged systems. See Figure 2 for an example of a vendor packaged system. For packaged system vendors with large numbers of components, a percentage of the final payment was tied to receipt of all the documentation.

A defined vendor management process was used for packaged equipment - *Table B*. This approach was applied to the purified water generation and the filter-dryer packages.

In a few cases, vendors did not initially receive the data and documentation requirements. The overall impact was increased C&Q and procurement time to follow-up with the vendor to get the required documentation.

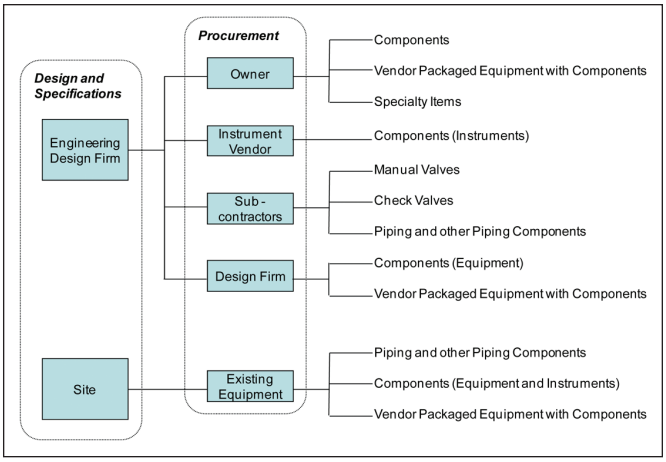

Figure 1. Procurement channels.

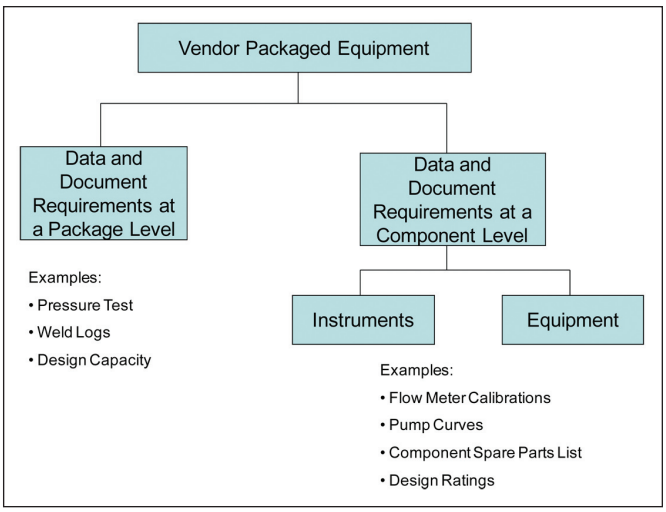

Figure 2. Vendor packaged equipment.

Learning Points:

1. Specifying data and documentation requirements from the beginning, following-up to make sure the vendors understood, and then making the final payment when all the requirements had been met proved very successful and solved the documentation gaps experienced in the prior two projects.
2. As in the prior two projects, when we did not communicate data and documentation expectations for a vendor upfront, we had difficulty getting the required documents.

Step	Activities
Request for Proposal	• Submit specifications, data, and document requirements
Bid/Pre-Bid Meetings	• Review of requirements/specifications • Review examples of vendor work including documentation • Discuss and resolve any exceptions
Vendor Selection	• Notification and set kick-off meeting prior to fabrication
Vendor Kick-off	• Visit vendor fabrication site • Review specifications and requirements • Inspect samples of work: field and documentation • Set and agree on inspection points
Fabrication	• In process weld inspections • Pre-FAT documentation checks
FAT – Factory Acceptance Test	• Final weld inspections • Final documentation checks • Final fabrication inspection • Software, controls checks • Operational testing • Final agreed upon punch list • Owner approval to ship
Shipment and Receipt	• Inspection for damage • Final punch list resolution • Final payment to vendor
SAT – Site Acceptance Test	• Arrange with vendor and complete SAT, if applicable

Table B. Vendor management for packaged equipment.

Construction

To address problems with construction quality in the prior projects, the project implemented a Construction Quality Assurance (CQA) program consistent with the ISPE Guide recommendations for Project Quality Control as a good engineering practice (Section 4.7.2). The program consisted of a lead individual and an assistant. The lead reported directly to the project manager and not the construction management team to remain independent from construction pressures. See Figure 3 for the reporting structure. In the prior projects, this quality assurance role did not exist.

The CQA program consisted of sharing key inspection aspects with the contractors, performing inspections of the first activities to assure alignment, and then performing periodic audits thereafter. In this manner, problems were prevented from the beginning. Early inspections indicated contractors did not understand the specifications, including how to complete required documentation of their work. These early findings led to appropriate conversations with construction quality control, sub-contractor foreman, and the owner inspectors to reach a common understanding and ensure work consistently met project standards. The project team felt this approach greatly reduced the overall number of field issues and facilitated system turnover, e.g., very few new issues at final system walk-down. Weekly meetings provided an effective forum to review findings and resolve quality issues with the sub-contractors.

A database tool provided a single source to track punch list items and was used to assist the CQA team in recording findings during the inspection process. It contained inspection checklists, the ability to attach and mark-up photographs, and track inspection findings and their close-out.
Some examples of where CQA made a difference included:

1. Assurance of proper gasket installation and maintenance from the beginning.
2. Clear documented evidence of pressure testing and passivation where required.
3. High quality turnover packages and quick resolution of documentation issues at mechanical completion.

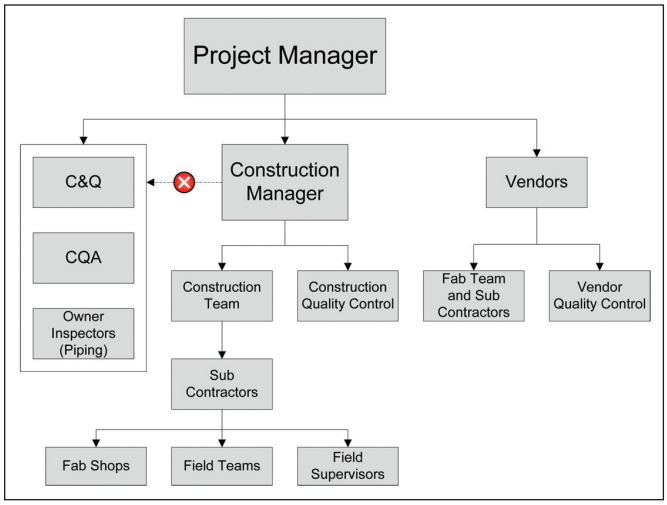

Figure 3. Construction oversight – construction quality assurance.

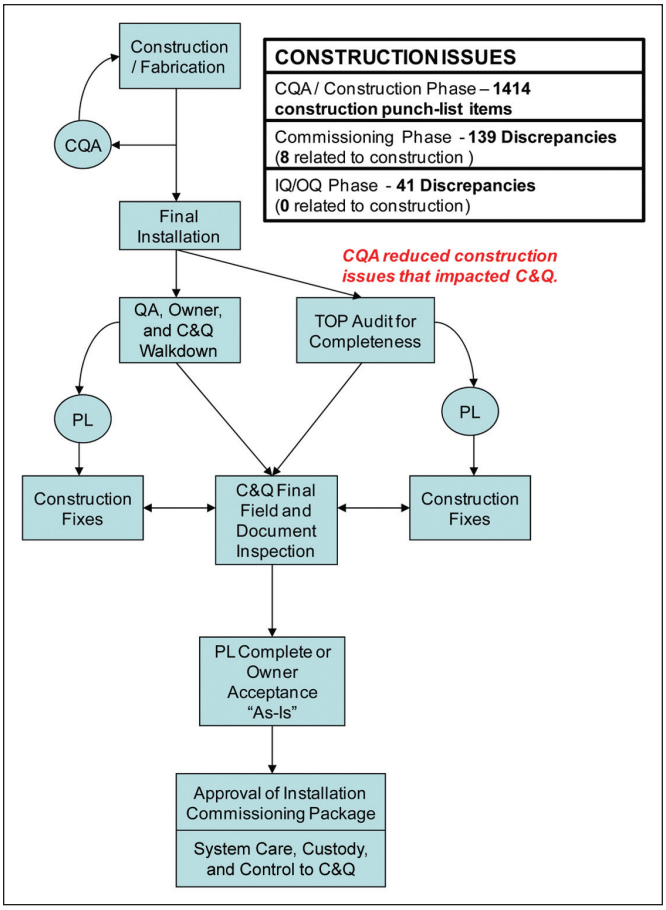

Figure 4. Construction and C&Q interface.

A system was not accepted as mechanically complete until the installation commissioning package was approved by the owner. Figure 4 provides a schematic of the process.

Learning Points:

1. The CQA program ensured quality processes were being followed from the beginning. Unlike the prior two projects where this role did not exist, construction issues were identified and resolved prior to beginning installation commissioning.
2. The database greatly facilitated issue resolution by tracking the issues in one place and providing clear evidence of the issue to be addressed.
3. The importance of the direct reporting to the project manager was critical as disputes over completeness occurred when schedules became tight.

Commissioning

The commissioning program provided the opportunity to ensure systems were operational and robust prior to qualification or release to operations. In the prior projects, the site had experienced the benefits of the commissioning program as defined in the Baseline Guides. So for this project, the C&Q team built on that prior success. The supporting elements for commissioning activities included:

Item	Description
Cost	• Additional upfront coordination and planning with automation
Benefits	• Elimination of testing duplication • Use of field testing to meet computer system validation and commissioning needs
Installation Check	Examples: • Not performing control panel or instrument wiring checks covered by automation checks • Leveraging dry loop checks to verify installation for commissioning and configuration for automation
Functional Testing (FT)	Examples: • No re-testing in the field of software interlocks and equipment control modules tested in the computer test lab to support computer system validation • Work with automation in development of FT protocols to ensure that testing of software interlocks and equipment modules that could not be tested in the lab are included in commissioning protocols

Table C. Integration of automation and computer system validation with commissioning.

- User requirements
- System and component level impact assessments
- Computer system validation requirements that needed integration with the physical system for testing and leveraging computer system testing. See Table C for more detail.
- EHS requirements. See Table D for more detail.

The goal of commissioning was to verify and document the installation and to safely start-up and test the equipment. Commissioning for this specific project consisted of two parts:

Item	Description
Cost	• Additional upfront verification and testing
Benefits	• Savings by eliminating the need for a separate EHS team to perform the verifications • Reduced risk of non-acceptance of systems by EHS in the late stages of the project
Installation Check	Examples: • Piping and equipment grounding and continuity tests • Accessibility of manual valves and manually operated equipment (ergonomics) • Pressure vessel inspections
Functional Testing	Examples: • Testing of hardwired safety interlocks and alarms • Testing of mechanically operated safety switches

Table D. Integration of EHS aspects.

INSTALLATION COMMISSIONING PACKAGE		FUNCTIONAL TESTING
Receipt Verification	**Installation Verification**	**Included Start-Up Activities**
• Verified that what was ordered was received without damage	• Verified acceptable field installation including a drawing walk-down of the installed system	• Executed filling and tuning of systems
• Confirmed acceptability of key engineering, EHS, and quality attributes. For example: - Materials of Construction - Surface Finish	• Field verified visible key aspects of installation for acceptability. For example: - Completeness of work without damage - Accessibility of components for maintenance	• Field tested functionality versus user requirements. For example: - Temperature Control - Pressure Control - Sanitization Cycles
• Verified key supporting documents were received and were correct. For example: - Material Certifications - Manuals - Spare Parts Lists	• Document verified aspects verified during installation but no longer visible. For example: - Gaskets - Weld Inspections	• Field tested functionality of hard-wired interlocks. For example: - High Level Switches - Emergency Stop Switches

Table E. Commissioning process.

1. Installation commissioning – verifying supporting documents and the acceptability of components received and the as-built state of the system.
2. Functional testing – verifying operational performance versus requirements.

The commissioning process steps are outlined in Table E.

Unlike the prior two projects, the availability of the required documentation and the quality of the construction allowed installation commissioning and construction to complete nearly finish-to-finish helping reduce the overall project timeline.

Functional testing took typically four to six weeks for major systems. Some examples of findings that increased the testing period included:

- Differences between the Factory Acceptance Test environment and the installed condition for packaged systems that required hardware and software modifications. For example at the site, the higher temperature of the supply water to the pre-treatment skid led to an extended cool down cycle following hot water sanitization of the carbon beds and in-turn caused the cycle to fail.
- Identification of design problems related to assumptions around the performance of used equipment and the capabilities of new equipment. For example, an existing tank had an oversized heating and cooling system that was not capable of meeting the desired fine temperature control without modification.

A dedicated team of automation, instrumentation, mechanics, and operators under the direction of C&Q provided efficient field repairs and accelerated testing progress. Vendor support with direct knowledge of the software and hardware was required to assist in the successful and timely start-up of vendor packages. When the functional testing was completed, the result was a fully tested, fully functional system.

Learning Points:

1. Understanding existing equipment capabilities was critical to overall success and ability to minimize schedule delays related to functional testing.
2. Proper planning and construction quality checks allowed installation commissioning for a system to be completed nearly finish-to-finish with construction.

Qualification

Using the risk-based approach presented by the ISPE Guide (i.e., system and component level classification) limited qualification activities to verifying and testing critical aspects of direct impact systems and their critical components. Table F provides an outline of the overall test plan. A key step in applying this risk-based approach was to clearly identify what was critical and get alignment from the stakeholders; primarily site engineering and site quality assurance. Systems were identified as direct, indirect, and no-impact following the guidance in the ISPE Baseline Guide.

Project Requirements Document	Testing/Verification to be Performed	Document Containing Results
• User Requirements • EHS Requirements • Design Documents (Drawings, Specifications, etc.)	• Verify Selected Component and System Attributes and Installation Features	• Receipt Verification • Installation Verification • Dry Loops • Calibration
	• Verify acceptable system start-up • Perform operational tests	• System Start-up • Functional Testing
• Product Quality Impacting Aspects of User Requirements and System Design	• Verify SISPQ impacting aspects of components and systems and their installation	• Installation Qualification
	• Verify SISPQ impacting aspects of equipment and system operation	• Operational Qualification

Table F. High level outline of the test plan.

"Unlike functional testing, which often took four to six weeks because of operational issues, operational qualification typically only took three days."

To support installation qualification, a component level classification was performed for direct impact systems to determine which components were critical and specifically what aspect(s) of the component made it critical. Unlike the prior two projects, this documentation on critical aspects was leveraged to limit the IQ verification checks to the critical aspects of critical components. This detail in the ISPE Guide (Section 3.3.5) of focusing only on critical aspects of critical components was not applied in the prior two projects. This resulted in all aspects of all components being subjected to verification in the Installation Commissioning phase and then the enhanced verification process in the IQ phase. By focusing only on the critical aspects of critical components, the size of the IQs and the execution time for this project relative to the prior two projects was significantly reduced. The IQ verification process fully leveraged the installation commissioning work and did not result in changes to the installed systems.

The operational qualification was a field execution of product critical tasks as defined in the user requirements. This was essentially a repeat of a subset of the tests performed in functional testing but under final conditions, e.g., approved software, implementation of final designs. Unlike functional testing, which often took four to six weeks because of operational issues, operational qualification typically only took three days. This testing went much better than planned and allowed C&Q and the project to fully catch-up and finish on schedule. As in IQ, the key difference in this project was to limit testing in the OQ to only the critical aspects versus repeating all testing performed in the FT as was done in the prior two projects.

Learning Points:

1. Component classification with a focus on their critical aspects effectively satisfied the scope of verification activities required for IQ and while reducing execution time.
2. Functional testing as a good engineering practice with qualification as a final controlled check worked extremely well and facilitated on time completion.

C&Q Manager's Perspective

Moving the site to the corporate large-scale C&Q delivery process required the full support of the site. It began with building trust with the site and understanding their needs. Creating alliances with key site influencers (process engineers, EHS, and quality assurance representatives) took the form of allowing adequate time for important discussions during the planning phase well before the time pressures of execution were present. Through these key influencers, the C&Q team had a trusted voice to site personnel. This added permanence to the agreed change and resistance to returning to prior practices and behaviors.

Alliances with key personnel also were critical during execution where differences in opinions and approaches became more visible. Further, having a site management representative, the project sponsor, dedicated to the project and residing in the project trailers helped the C&Q team gain ready access to an influential site person who had a solid understanding of the project and site issues.

Part of sustaining acceptance of the changes also meant that the project tools the C&Q team used had to be seen as working correctly. For example, the database containing the component information had to be maintained so the data was accurate. By doing this, data errors in form generation were prevented. Another example was the document review and approval process. To get support from the team for the single review and approval cycle, the document generation processes had to produce high quality documents with almost no typographical errors and very few technical content gaps from the beginning. These types of activities built a high degree of trust and confidence in the processes that were being used. Finally, having a full time corporate level C&Q representative demonstrated a commitment to see the project through and own the issues that arose during implementation and execution of the program.

Learning points:

1. Establishing trust required a technically sound program and the personnel capable of creating effective relationships. The program being presented had an established record of success and the C&Q team had established credibility with personnel at the site who were considered technical experts.
2. Cultural change was effective because the site and the project team wanted to make improvements. This created an open environment of trust and teamwork from the beginning.
3. The presence of a dedicated site management person and a dedicated corporate level C&Q manager from beginning to the end of the project provided the continuity to see the program through and effectively address issues as they arose.

Summary

Successful C&Q execution was driven by using a proven process, dedicated technical expertise, and teamwork. Cost and schedule objectives were met. The C&Q cost, including CQA costs, was 5.8% of the Total Installed Cost (TIC) for the project. The high percent of TIC reflected the large amount of work for C&Q on existing equipment that was not included in the total project cost. Ultimately, the C&Q costs came in at 93% of the estimate provided at the end of basic engineering. Regarding schedule, the time from the last mechanical

completion to turn over of all equipment to the site was 90 days. C&Q activities were completed per schedule and on time for Process Validation.

Some of the key successes and leveraging of best practices were:

- *Building on past lessons learned from the site.* As a team, the project and the site looked for a better way to deliver projects. A key outcome from this was a dedicated site representative at a management level for the project and a dedicated company C&Q lead for the project.
- *Adoption of the corporate large scale delivery processes, the ISPE Baseline Guide approach.* Showing how it addressed the site's needs greatly facilitated its acceptance by the site. Focusing on critical aspects only during qualification reduced the project timeline.
- *Implementation of CQA.* Construction issues were found early and corrected.
- *Resourcing of key C&Q staff upfront.* This ensured that data and document requirements and user requirements were defined early in the project.
- *Integration of activities with safety and automation.* This minimized duplication and leveraged testing and resources.

This case study presents how teamwork and following the principles set forth in the ISPE Baseline Guide for C&Q can be used to overcome typical project challenges and effectively deliver an on-time, on-budget, and well-tested facility to the client.

Glossary of Terms

API Active Pharmaceutical Ingredient

C&Q Commissioning and Qualification

CQA Construction Quality Assurance

EHS Environment, Health, and Safety

FAT Factory Acceptance Test

FT Functional Testing

GEP Good Engineering Practice

IQ Installation Qualification

IV Installation Verification

OQ Operational Qualification

P&ID Piping and Instrument Drawing

PL Punch List

QA Quality Assurance

RV Receipt Verification

SISPQ Safety, Identity, Strength, Purity, and Quality

SME Subject Matter Expert

TOP Turn Over Package

Vendor Packaged Equipment Skid mounted equipment provided as a package typically with the vendor's control system, e.g., a purified water generation skid

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1. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5 – Commissioning and Qualification,* International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2001, www.ispe.org.

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