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# PHARMACEUTICAL ENGINEERING®

THE OFFICIAL MAGAZINE OF ISPE

NOVEMBER/DECEMBER 2009 VOLUME 29, NUMBER 6

## Science- and Risk-Based Verification

## Quality Risk Management Principles

## Pharmaceutical Manufacturing and Product Quality

## Risk-Based Qualification

## Construction Quality Management

## Interview with

Jon Clark, CDER Office of Pharmaceutical Science (OPS), FDA
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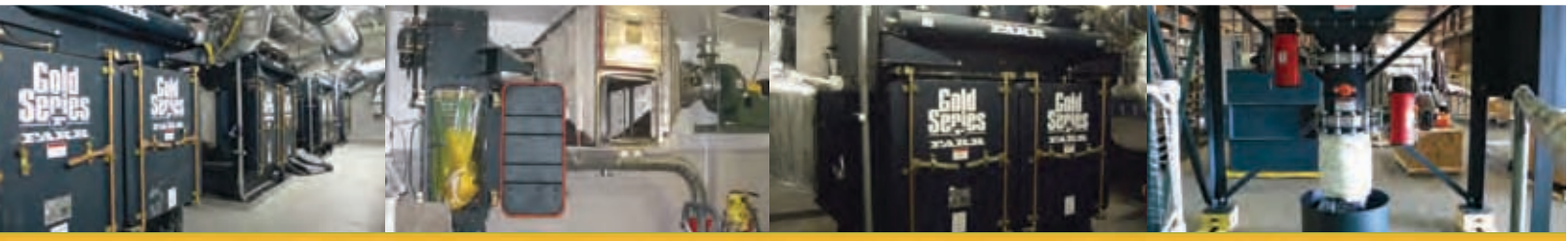

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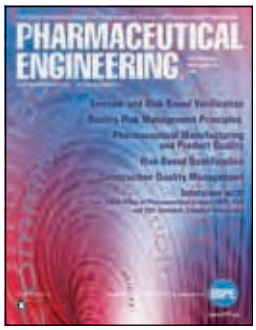

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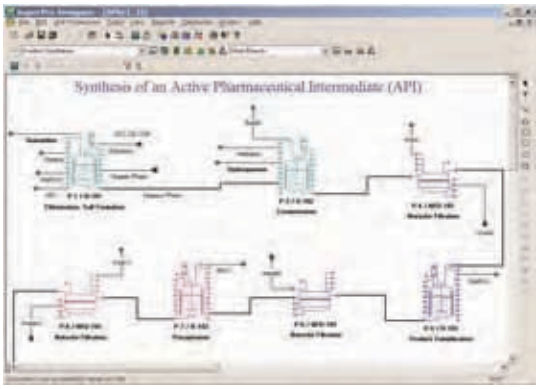


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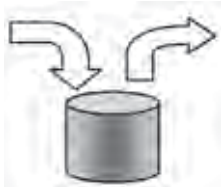


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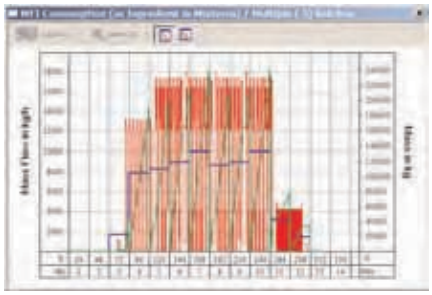

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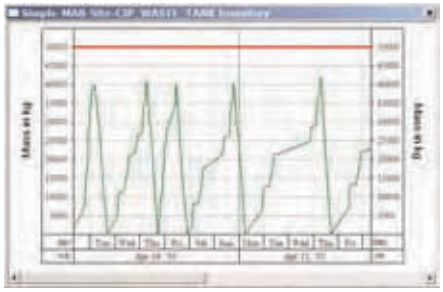

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**This article describes the approach for implementation of the ASTM E2500 standard in Pfizer to enable a cost-efficient and lean approach to science- and risk-based verification.**

# Commissioning, Qualification, and Verification – Lean Approach to Implementation

by Nicholas Andreopoulos, Gert Moelgaard, Sabra Seyer, and Graham Wrigley, PhD

When the existing ISPE Baseline® Guide for Commissioning and Qualification (Volume 5) was launched in 2001, it gained broad acceptance in pharmaceutical companies around the world and has been widely applied as the reference for a more streamlined approach compared to the older concepts of validation that were used quite differently in various companies.

The Baseline® Guide introduced a few key concepts and there have been significant improvements in the application of C&Q. Companies have established Good Engineering Practices (GEPs) and in doing so, increased the ability to leverage commissioning tests into Installation and Operational Qualification (IOQ). The impact assessments also have been very effective in identifying the manufacturing systems that have direct impact on product quality.

Many companies have realized that even today's practices of C&Q are still quite expensive and time consuming and do not focus on the opportunities afforded by a science- and risk-based approach. A significant effort has been undertaken within some companies to streamline the C&Q tools and practices, and there have been resulting improvements. With the establishment of Good Engineering Practice (GEP) and Quality Risk Management principles, there are new opportunities to rethink current practices.

In May 2007, the ASTM Committee E55 on "Manufacture of Pharmaceutical Products" approved the ASTM E2500 "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment." This was the starting point of an industry transition toward a science- and risk-based approach to Commissioning and Qualification.

ASTM E2500 changes the focus of C&Q. Where the C&Q Baseline® Guide focuses on each manufacturing system with its system and component impact assessments, the ASTM E2500 Standard enables a verification approach focused on the product/process requirements and risks to product quality and patient safety.

The E2500 standard was originally initiated by ISPE's International Leadership Forum to leverage the principles of Quality Risk Management as outlined in the Q9 Guideline from International Conference of Harmonization (ICH). Since the ASTM E2500 Standard was approved, a number of articles have been written and presentations given which has resulted in a lot of discussion on its application. It is now becoming the core content of the ISPE Baseline® Guide on Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment.

The application of the ASTM E2500 Standard and the new ISPE Baseline® Guide based on E2500 is a natural progression toward a streamlined science- and risk-based activity that ensures the 'fitness for use' of a manufacturing system in a significantly more cost-effective way than traditionally applied. 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.

## E2500 Verification as a Lean Approach

When the ASTM E2500 Standard was approved, it was seen as a major breakthrough by some

*Continued on page 10.*

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*"The term Verification was selected to enable and describe how the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk to the patient – and specifically applies it to the Verification effort."*

companies whereas other companies seemed hesitant to apply it – especially companies that were not familiar with the Quality by Design (QbD) and Quality Risk Management principles.

However, over the past year, many companies are starting to apply Quality Risk Management for new and existing products. Companies have seen what a useful tool a well conducted Quality Risk Assessment based on product and process knowledge can be. When applied to verification activities, it really helps focusing the main attention of the verification activity to those aspects of the manufacturing systems that are critical to product quality and patient safety.

Within Pfizer a lean project was established in 2007 to challenge the current C&Q approach. This project was led by representatives from the Global Engineering, IT, and Quality groups, and was sponsored by Pfizer leadership. The primary focus of the project is not just the implementation of new standards or tweaking of the current C&Q approach, but a re-evaluation of the C&Q process to have a step change improvement in cost and schedule efficiency. The intent was to continue on the C&Q enhancements that were implemented at Pfizer sites and to use the ASTM E2500 as an enabler of the next level of C&Q improvements.

The lean approach also was utilized to ensure that the issues with the current C&Q approach are addressed with the new process and to establish metrics to confirm the process improvements.

The first step of the lean project was to obtain feedback from the organization on C&Q execution issues. This defined the C&Q issues which were addressed as part of the lean project. The feedback from the organization identified important business challenges, such as:

- overall C&Q process is too complex with numerous documents, steps, and reviews
- lack of process scaleability and flexibility in the approach
- lack of integration with other systems (i.e., automation)
- lack of consistency in the application of system- and component impact assessments across the organization
- need for clarification or redefinition of roles and responsibilities in C&Q projects
- overdoing leveraged commissioning efforts because some commissioning may become part of the qualification documentation

The ASTM E2500 standard and ICH Q8/9/10 concepts can be used to address some of these issues and enable a streamlining of the C&Q process into an overall Verification program.

## ASTM Verification Approach versus Qualification

The core concept of ASTM E2500 is described with the term **'Verification.'** The standard deliberately avoided the terms *'Qualification'* and *'Validation'* to signify an intentional departure from past practices.

The term Verification was selected to enable and describe how the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk to the patient – and specifically applies it to the Verification effort.

In traditional C&Q, some companies ended up applying the rigid Qualification methods, level of documentation, and Quality Unit approval to most of their facility project documents, despite the impact assessment process. This resulted in technical details being included in large, highly prescriptive protocols and significant efforts for both Commissioning and Qualification. For those companies, the distinguishing between commissioning and qualification was lost and C&Q did not lead to the anticipated savings.

Some of the companies that have applied the C&Q method, as well as the previous GAMP approach to computer system validation, have been executing parallel programs leading to repetitive testing of the same features and functions.

The scope of Verification is broad and the approach is relying on *Good Engineering Practices (GEPs)* and other supporting principles as described in the E2500 Standard. Accordingly, the scope and extent of the verification activities where the Quality Unit should be involved are mainly in areas of potential risk to the patient safety and product quality, i.e., the Critical Aspects of the manufacturing system.

Previous C&Q practices have a missing link between the impact and the actual risk to quality, safety, and efficacy of the drug product, which the ASTM E2500 addresses. There is a need for a change, to a focus on product quality, safety, and efficacy and to a focus on a verification approach based on Good Engineering Practices, Quality Risk Management, and a few other supporting activities.

## Quality Risk Management and Verification

The key to successful Verification of a facility project is a clear Quality Risk Management approach. For *new* pharmaceutical products developed by Quality by Design (QbD) principles, this is largely done as part of product development and registration, but for *existing* products (*legacy* products), it has to be deduced from other sources, including the available process development documentation, process validation packages, and the manufacturing history.

The main focus of the Verification effort is put on the *Critical Aspects* of the manufacturing system, meaning the functions,

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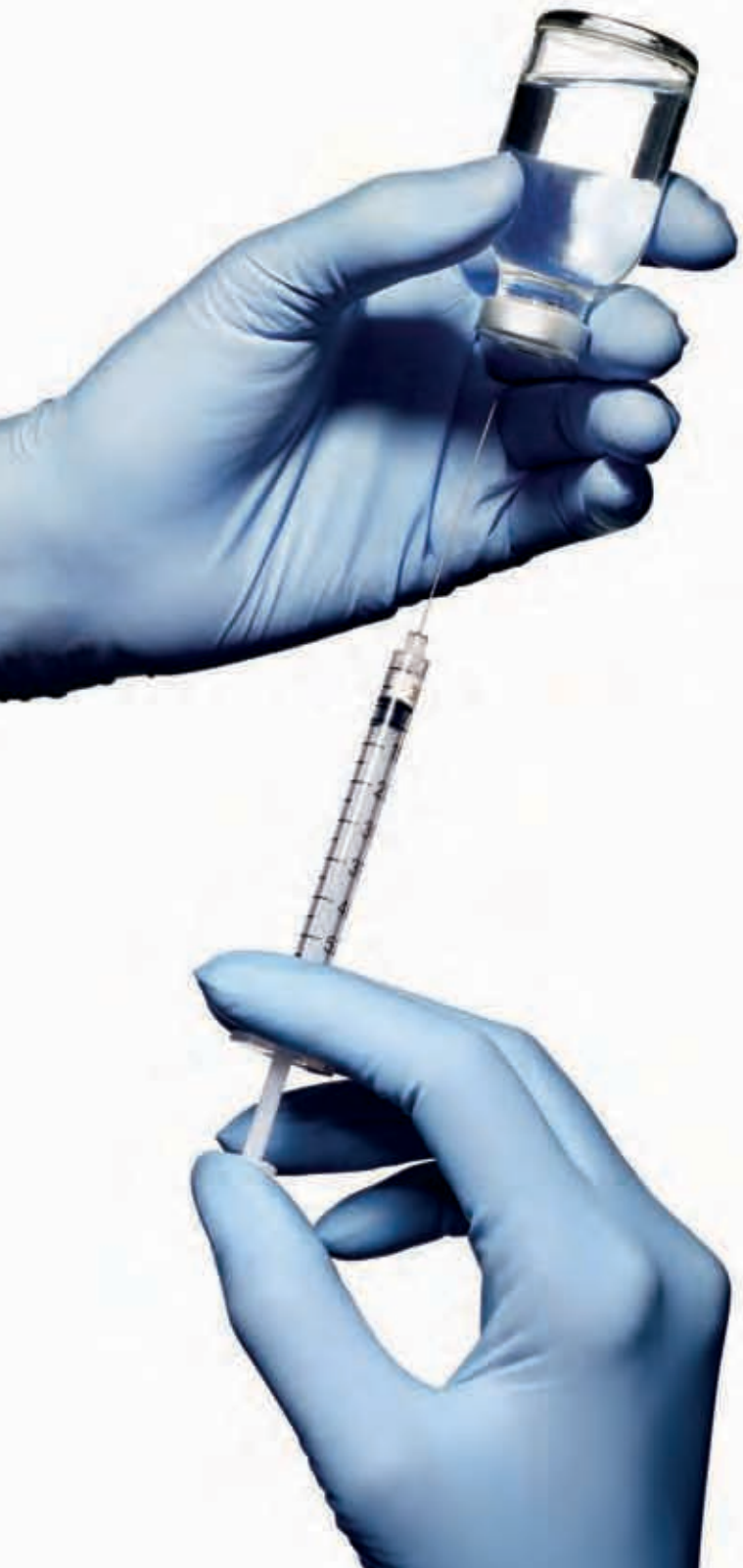

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features, etc. necessary for the manufacturing process and systems to ensure consistent product quality and patient safety. The Critical Aspects should be identified based on scientific product, process understanding, and system knowledge, as well as on regulatory or company quality requirements.

Since the verification activities focus on the Critical Aspects of the manufacturing system and all testing is done according to Good Engineering Practice (GEP), the new approach can lead to significant savings in capital projects. Once the Critical Aspects are identified and the core principles of the verification approach are well understood, a verification project should be easier and more cost-effective to execute than a traditional C&Q execution.

The basis of this thinking comes directly from core principles in ICH Q8 and Q9:

*ICH's Q8 Guideline on Pharmaceutical Development* gives a *scientific* basis for the Verification approach by defining core concepts for pharmaceutical product and process characterization, which focuses on the patient through Critical Quality Attributes (CQAs) of a pharmaceutical product and the related Critical Process Parameters (CPPs) that are used to control its manufacturing process.

- The evaluation of the quality risk should ultimately link back to the potential harm to the patient.

- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

The combination of these principles are core to a science- and risk-based approach and core to ASTM E2500 verification together with a number of supporting activities, such as Good Engineering Practices, design review, risk management activities, engineering change management, and the leveraging of vendor activities.

When used as intended by the E2500 standard, one can save resources without increasing the compliance risk. The verification approach encourages starting Quality Management activities much earlier in the process than the previous C&Q approach. It also encourages risk mitigation practices to design out risk, where possible, in the manufacturing system.

However, the verification approach must be combined with a set of well established Good Engineering Practices that address the fundamental quality assurance of robust and

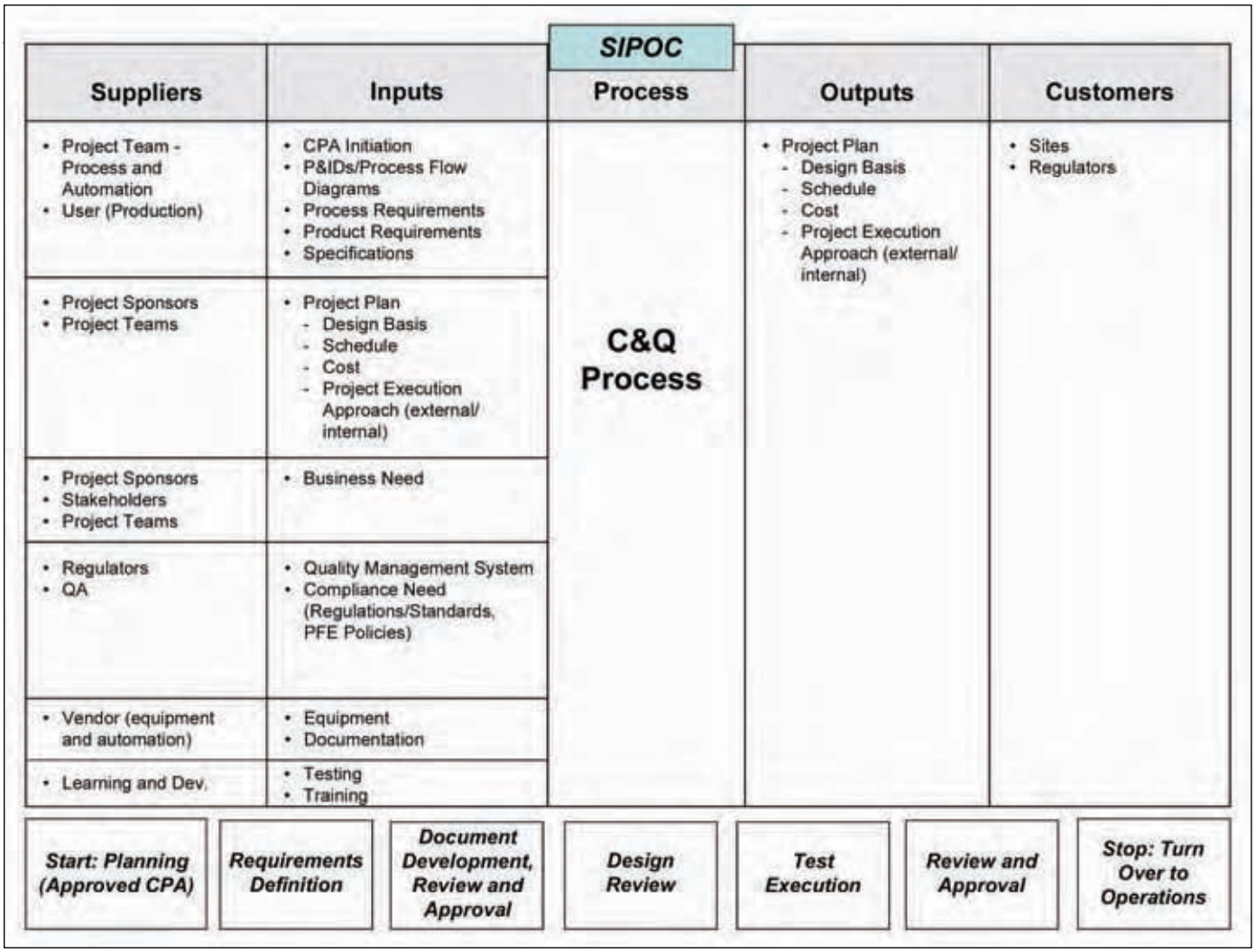


Figure 1. Pfizer Suppliers, Input, Process, Output, and Customer (SIPOC) analysis of the C&Q process.

well documented engineering, construction, and verification of a manufacturing system during its lifecycle. This includes good testing practices, good documentation practices, and an engineering change management system that can manage changes during the construction, installation, and verification phases.

## Applied Manufacturing Science

The risk assessments as well as the identification of Critical Aspects are the areas where the Quality Unit involvement is important. The Quality Unit may be involved in other activities, but at least here they must be involved. Quality also should be involved in the overall risk assessment and the verification planning. The rest of the activities should ideally be controlled by GEP, other subject matter experts, and through the leveraging of vendor test documentation.

The ASTM E2500 approach, which now has become the shared basis between the upcoming ISPE Baseline® Guide for Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment and the new GAMP® 5 guide, encourage focus on the Critical Aspects and the elimination of repetitive testing.

## Transformation to E2500 Verification

The transformation from C&Q to E2500 Verification is more than just changing practices and procedures. Within a pharmaceutical company, it requires change in roles/responsibilities, buy-in from key stakeholders, and the ability to quantify the benefit of change.

At Pfizer, our Right First Time program for continuous improvements enabled us to lead the C&Q transformation. The lean project team had colleagues from key stakeholder functions and global sites. The Pfizer lean project method includes the following stages: Define Measure, Analyze, Recommend, and Act. We developed value stream maps for the current and future state and analyzed the current issues with C&Q as mentioned above.

The final new process was reviewed against these current issues to make sure they are all addressed in the new process. Furthermore, we defined a so-called Suppliers, Input, Process, Output, and Customer (SIPOC) analysis of the C&Q process, as shown in Figure 1.

Status today is that a new Pfizer verification process has been designed based on ASTM E2500. We have completed three pilot projects on the new process at a number of Pfizer sites in parallel to developing the guidelines for the new ASTM-based process. To date, we identified average savings of 13% of C&Q costs – just through a reduction of activities and documentation. Additional streamlining opportunities in the execution of testing is being identified and assessed as part of our implementation plan. We will continue to use cost, quality, and schedule metrics to monitor the improved efficiencies of the new approach.

*Concludes on page 14.*

## Conclusion

What Pfizer, like many other companies, have experienced, is that the traditional C&Q approach is more extensive, expensive, and time consuming than necessary. The traditional approach on all direct impact systems has led to more inspection, testing, rigid change management, and other activities than necessary to achieve regulatory compliance. Most of this effort can be replaced by GEP and can be controlled by the appropriate subject matter experts who are defined within the project team.

The focus on risk to the patient and the flexible verification approach with active involvement of vendors can save resources without increasing the compliance risk. By moving much of the qualification activities to GEP, combined with good testing practices, good documentation practices, and engineering change management, significant savings can be achieved without decreasing quality or increasing regulatory risk.

We encourage companies to use the new verification approach in driving a lean approach to C&Q. Our experience to date has shown C&Q cost savings related to a reduction in documentation and test activities. Actual project savings vary depending on a site's current implementation of GEP, and application of science- and risk-based concepts in defining the manufacturing system Critical Aspects.

We are currently rolling out the new Verification approach beyond the current pilot projects and we look forward to sharing learning and experiences with other companies applying the ASTM E2500 principles. So far, it is our experience that once the concepts of the Critical Aspects are well understood, the remaining activities are a logical progression of C&Q concepts, combining Lean thinking with Good Engineering Practices and Quality Risk Management principles.

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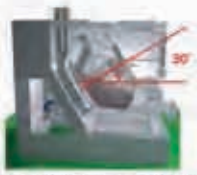


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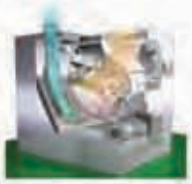

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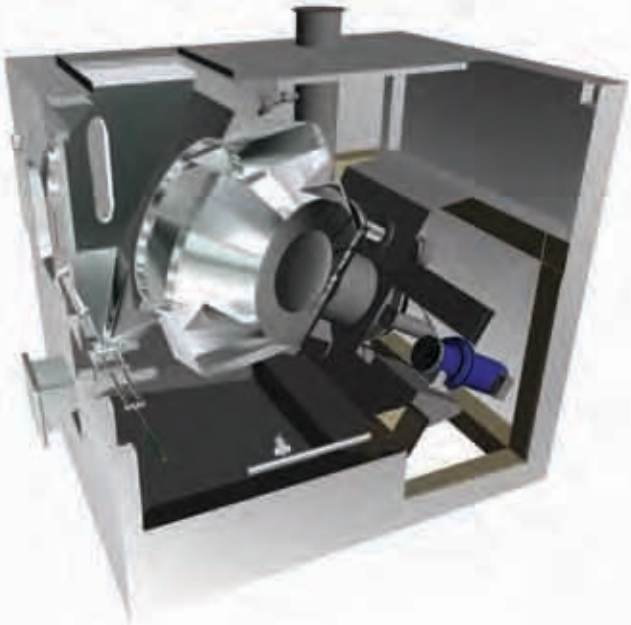

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# Applying Quality Risk Management Principles to Achieve a Practical Verification Strategy

by Ian Campbell

**This article presents a practical application of Quality Risk Management for the extent of verification necessary during Factory Acceptance Testing (FAT), Commissioning and Qualification (C&Q).**

## Introduction

This article provides the optimum requirements for Factory Acceptance Testing (FAT) and Commissioning and Qualification (C&Q) of equipment for compliance with current Good Manufacturing Practices (cGMPs) as mandated by the US Food and Drug Administration (FDA), EMEA, and Health Canada. The requirements also are consistent with the International Conference on Harmonization (ICH) Guidelines.

A Quality Risk Management (QRM) approach to verification focuses on critical attributes of the equipment as they relate to product performance and their relevance to quality, strength, purity, safety, and efficacy. The strategy is based on the degree of comprehension of the manufacturing controls and quality systems. This will allow for fewer restrictions when purchasing new equipment.

Three levels of risk classification are outlined in this article, which have been aligned with GAMP® 5 classification (high, medium, and low) applying the principles of Failure Mode and Effects Analysis (FMEA), where severity, likelihood of occurrence, and detectibility are quantified to evaluate the overall risk. All equipment can then be categorized based on criticality. General verification requirements were established to serve as a guide.

The assessment of equipment criticality or risks classification determines the requirements for verification and at what step in the procurement process they should be done, i.e., FAT versus commissioning versus qualification; depending upon the risk category assigned.

The focus of effort is then placed on verifying the most critical parameters to demonstrate that the equipment is under adequate control for the critical process parameters. New equipment will be assessed using this tool and the appropriate actions will be taken to ensure efficient compliance.

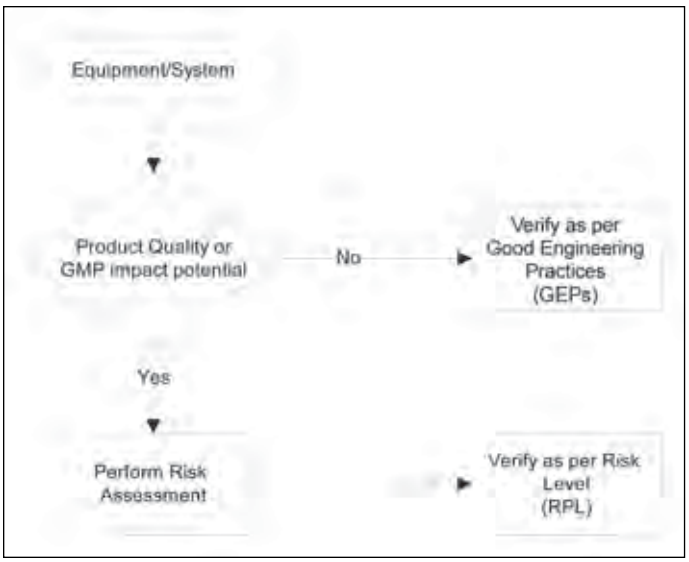


Figure 1. The assessment was based on quality and GMP risk. Any risk for disruption of business will be factored in as a discretionary decision as to the level of documentation required and should otherwise be based primarily on good engineering practices.

## Strategy

The implementation of the QRM framework requires an educated, well-trained, and integrated team of Subject Matter Experts (SMEs). Expert opinions from engineering, operations (manufacturing), validation, and quality operations were used to assess the appropriate critical to quality risk indicators and to assign the risk levels.

All equipment is first assessed and evaluated against the supporting cGMP systems in place, such as the necessary maintenance, calibration routine, procedural

*Continued on page 18.*

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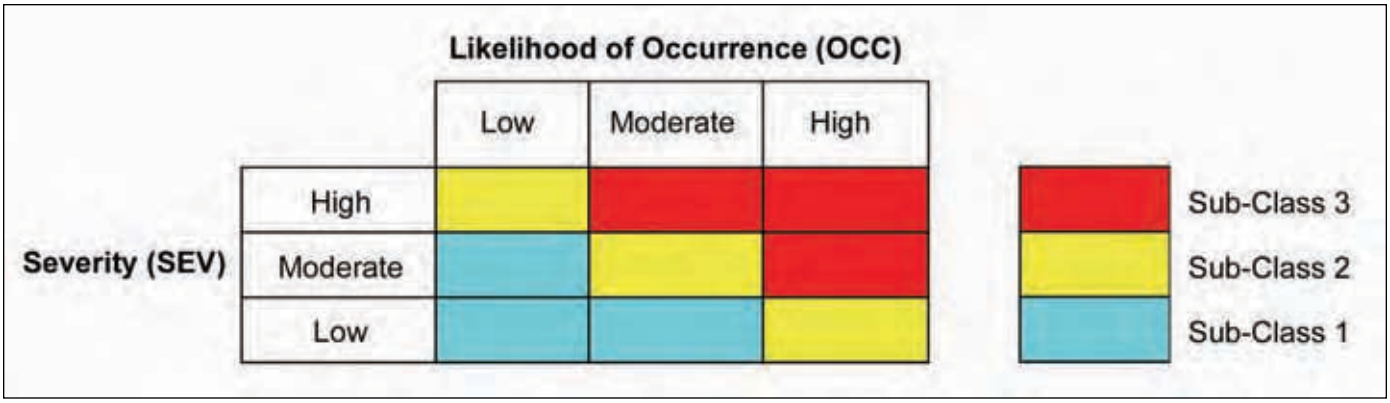


Figure 2. "Severity" (SEV) vs. "Occurrence" (OCC) to obtain "Sub-Class."

controls, etc. These cGMP systems enable a continued support to the initial and continued state of qualification/verification. All available information and data is formulated to estimate the probability of the worst possible problem (failure) occurring. A further assessment is then performed to characterize the risk and establish a guideline for a verification plan.

A three step process is undertaken to determine the necessary verification activities and when they can be performed.

## Categorization of Equipment

The equipment is first evaluated based on the complexity of operations and the critical parameters to which they are subjected. Although the systematic evaluation of risk should be as exhaustive as possible, additional observations may be added where appropriate, in order to accommodate specific equipment or compliance requirements.

The equipment should be separated into categories or types based on unit of operation. The categorization is done based on operating principles and design characteristics. In some cases, the particularities of the unit operation within a given equipment category may require further division into subclasses. For example, a balance used to weigh loaded pallets prior to shipping should be treated differently (separated into a different category) than an analytical balance used to dispense raw materials to be processed in a batch of drug product.

## GMP Impact Assessments

Each category of equipment should then be evaluated against specific, pre-established criteria to determine if the equipment or any part of it could potentially impact the quality of product or patient safety and hence, impact cGMPs. If the impact assessment determines that there was no potential for the equipment to impact product quality or GMPs, the equipment is not evaluated further, but falls under the scope of Good Engineering Practices and verifications required for non-GMP purposes.

Any equipment that is judged to have a potential impact on the product or GMPs should undergo a risk analysis to determine the associated level of risk. A thorough analysis of the operating principles and design characteristics of each equipment is performed by a team of highly trained, professional Subject Matter Experts (SMEs) in order to determine the worst potential failure of that category of equipment. The worst case failure can be evaluated using the GAMP 5[1] model of FMEA. The necessary verification requirements can then be determined with the level of risk.

## Risk Assessment

A Risk Priority Number (RPN) is established based on the overall risk of failure as indicated by the likelihood of occurrence, detectibility, and severity. Equipment should be ranked based on the potential risk of failure as it translates to the end user (or patient) by an erroneous result. Different categories

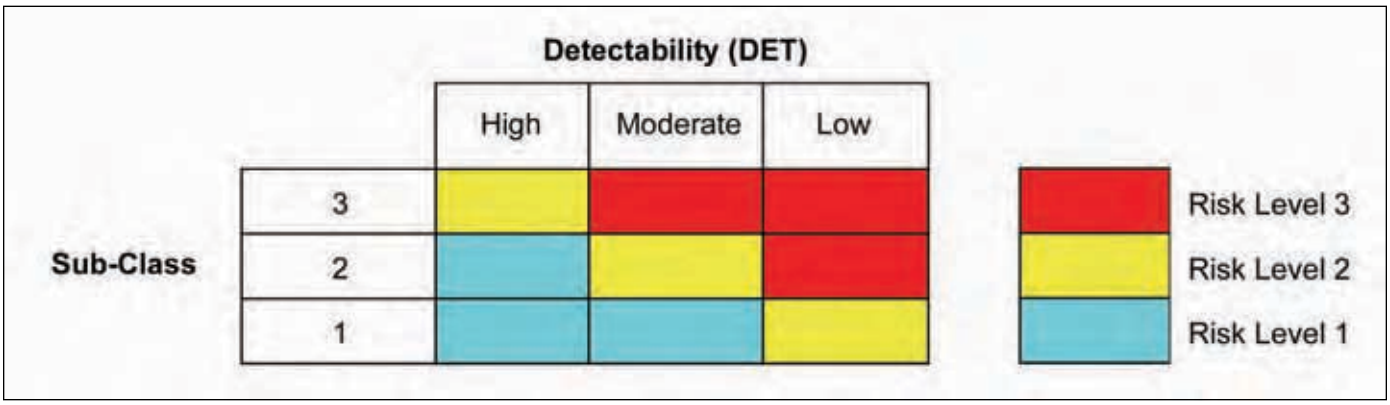


Figure 3. "Sub-Class" vs. "Detectability" (DET) to obtain "Level of Priority." Reference ISPE GAMP 5 (Adaptation).

*Continued on page 20.*

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| Risk Level | FAT Requirements | Commissioning Requirements | Post Commissioning Installation Verification | Post Commissioning Operation Verification |
|---|---|---|---|---|
| 3 | • Ensure equipment meets design specifications as per User Requirements Specifications (URS) and Purchase Order (PO).<br>• Define and perform extensive operational testing as per URS.<br>• Run simulation of actual application if possible. | • Verify that the equipment has been entered in the site systems.<br>• Perform operational tests as outlined in the URS.<br>• Perform extensive testing simulating actual application. | • Verify that commissioning tests were completed as required.<br>• Verify that necessary systems are in place.<br>• Verify specific items as indicated. | • Testing of primary equipment functions as defined in the URS.<br>• Testing of equipment auxiliary functions, due to their complexity and their direct impact on product quality.<br>• Verify that commissioning tests were completed as required. |
| 2 | • Ensure equipment meets design specifications as per URS and PO.<br>• Define the necessary operational tests as outlined in URS. | • Verify that the equipment has been entered in the site systems.<br>• Perform operational tests as outlined in the URS. | • Verify that commissioning tests were completed as required.<br>• Verify that necessary systems are in place. | • Testing of primary equipment functions as defined in the URS. Note: It is necessary to document a rational for testing or not testing certain functions.<br>• Verify that commissioning tests were completed as required. |
| 1 | • Ensure equipment meets design specifications as per URS and PO. | • Verify that the equipment has been entered in the site systems. | • Verify that commissioning tests were completed as required. | • Verify that commissioning tests were completed as required. |

Table A. Overview of verifications per level of risk.

of risk should be aligned with FMEA principles using the risk assessment method outlined in GAMP 5 to provide for a systematic evaluation.

Each risk evaluated is meant to represent the highest overall risk potential for any failure that may occur. Each risk component was evaluated as outlined in the GAMP 5 risk assessment method in order to establish its likelihood of occurrence, severity, and detectibility. These categories are

| Test | Factory Acceptance Test (FAT) | Commissioning (COM) | Equipment Validation (VAL) |
|---|---|---|---|
| Equipment Identification | Verify | Verify | Refer |
| Product Contact Parts Verification | Define | Document | Verify |
| Equipment and Major Component Verification | Define | Verify | Refer |
| Visual Inspection | Verify | Verify | Verify |
| Company Specific Requirements | Fine Tune | Verify | Refer |
| Space Allocation | Define | Verify | Refer |
| Environmental Conditions | Define | Verify | Refer |
| Documentation Availability | Verify | Verify | Refer |
| Drawings, P&ID, etc. | Define | Verify | Refer |
| Purchase Order | Define | Verify | Refer |
| Computer/Automation Requirements | Define | Document | Verify |
| Access Level Verification | Define | Fine Tune | Verify |
| Input and Output Verification | Verify All Critical | Verify Representative% | Refer |
| Control Switches Operation Verification | Verify | Verify | Refer |
| Alarms and Interlocks Verification | Verify All Critical | Verify Representative% | Refer |
| Backup of the Application Software Verification | Draft | Fine Tune | Verify |
| Electronic Signature Verification | Define | Fine Tune | Verify |
| Electronic Record Verification | Define | Fine Tune | Verify |
| Equipment Safety Features Verification | Define | Fine Tune | Verify |
| Equipment Utilities Verification | Define | Verify | Refer |
| Power Failure Recovery/Surge Verification | Define | Verify | Refer |
| Equipment Preventive Maintenance Verification | Define | Fine Tune | Verify |
| Standard Operating Procedures Verification | Draft | Fine Tune | Verify |
| Radio Frequency Interference (RFI) | Define | Fine Tune | Verify |
| Instrument Calibration Verification | Define | Calibrate | Verify |
| Reject System and Fail Safe Verification | Define | Fine Tune | Verify |
| Functionality Testing | Verify Representative% of Functionality Tests | Verify Representative% of Functionality Tests | Functionality AQL – 100% |
| Performance Testing (where required) | Define | Fine Tune | PQ or Demo Verify |

Table B. Timing of verification.

then factored together to provide an indication of the overall risk as defined by the Risk Priority Number (RPN).

The RPN is then used to determine the required level of effort involved in the equipment FAT, Commissioning and Qualification. The equipment is then classified into three different categories based on their associated level of risk. This granularity will serve to ease the decision making process for the required level of qualification to be applied to any equipment. This approach is intended to serve as a guide and may be adjusted if required to suit any particular characteristic of a given piece of equipment. The categorization of the equipment allows us to determine the scope and extent of verification required as well as any other deliverables judged necessary.

Risk Priority Numbers (RPNs) for risk classification by levels of criticality are assigned for each equipment type based on several factors which include, but are not limited to:

- the degree of operational understanding or history
- the relative robustness of supporting systems
- the relative robustness of the process controls
- the relative complexity of equipment
- degree of variability of the equipment and controls used to detect variability

The RPNs are established for worst case failure that could potentially impact the strength, safety, purity, quality, and identity of the product. Considerations should be given to many of the supporting systems that serve as indicators of control, such as in process checks, calibration requirements, re-qualifications etc., as well as experience in using a given type of equipment, and any trends evident from investigation reports.

The severity of a given failure in relation to potential impact to product quality and GMPs is evaluated by the multidisciplinary team classified as high, medium, or low. The likelihood of occurrence for the given failure is then evaluated as high, medium, or low. The severity is compared against the likelihood of occurrence to determine the subclass of risk - *Figure 2*. This value is subsequently used to compare against the detectibility of the event in order to determine the overall risk associated with the failure.

The subclass determined from the previous step is then compared to the detectibility to determine the overall level of risk for the worst case failure. The associated level of risk is then ranked as a Risk Priority Level (RPL) as either low (1), moderate (2), or high (3).The risk levels are related to the impact on product quality and GMPs - *Figure 3*.

## Risk Priority Number (RPN)

### *Risk Level 3 – Highest Risk*

Equipment that generally have direct impact on product quality and/or GMPs are considered the highest risk. These are representative of the most complex equipment used. All Level 3 equipment will require an extensive verification, encompassing the entire range of operating parameters required for equipment use. The particular requirements and deliverables are outlined in Table A.

### *Risk Level 2 – Moderate Risk*

Equipment that generally have indirect impact on product quality and/or GMPs are considered moderate risk. These are representative of the moderately complex equipment used in the manufacture, packaging, or holding of drug products. Level 2 equipment require a less extensive verification and number of deliverables. The particular requirements and deliverables are outlined in Table A.

### *Risk Level 1 – Low Risk*

Equipment that have negligible impact on product quality and/or GMPs are considered low risk. These equipment are generally not the most complex used in the manufacturing, packing, or holding of drug product. Category 1 equipment will require a less extensive qualification study and number of deliverables. The particular qualification requirements and deliverables for category 1 processes are outlined in Table A. Control is ensured primarily through routine procedural controls as well as the normal supporting systems, e.g., calibration and Project Management.

## Verification

A comprehensive list of verifications to be undertaken is then created to ensure that the necessary controls are in place to maintain the quality, purity, identity, strength, and safety of our drug products and to respect all regulatory requirements. This is confirmed through the necessary approval of

*Concludes on page 22.*

*"The main objective of equipment verification is a reduction in variability through equipment and process understanding … QRM provides an effective approach to establish a scientific basis for the required verification effort."*

documents outlining the acceptance criteria approved by the required SMEs and quality unit for any system containing critical to quality aspects.

The necessary verifications and the level of detail required are determined based on the Risk Priority Number (RPN). The timing of each verification is then established so as to ensure resource optimization and to avoid unnecessary duplication. An outline of the recommended timing of activities that must be verified is presented in Table B. This list is not meant to be restrictive and should be evaluated throughout the project lifecycle.

## Conclusion

A systematic approach to verification through the application of QRM principles enables pharmaceutical manufacturers to apply an efficient approach to compliance in an increasingly complex manufacturing environment. The application of QRM principles as outlined in this article will allow for there to be a maximum compliance level by focusing verification on the critical to quality attributes with the most efficient use of resource through a systematic and scientifically sound approach.

The main objective of equipment verification is a reduction in variability through equipment and process understanding (e.g., application of knowledge throughout the equipment lifecycle). QRM provides an effective approach to establish a scientific basis for the required verification effort.

Application of this enhanced science and engineering knowledge in decision-making will improve the efficiency and effectiveness of the verification effort, allowing manufacturers to use valuable resources in a more efficient manner.

The approach outlined in this article will allow for much efficiency to be realized through a standardized process of performing the appropriate test at the appropriate time eliminating any unnecessary duplication. The primary focus remains the same: to assure the maximum amount of control over pharmaceutical product manufacturing and packaging operations.

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**This article reviews the latest FDA philosophy to enhance and modernize the regulation of pharmaceutical manufacturing and product quality, which is perhaps best captured in two mottos: "Know Thy Process" and "Know Thy Risk."**

# Pharmaceutical Manufacturing: How to Understand the Process and Assess the Risks to Patient Safety

by Robert Jones

## Introduction

At the entrance to the Temple of Apollo, at Delphi, there was a famous inscription, commonly translated as, "Know Thyself." It was adopted by the philosopher Socrates (470 BC – 399 BC) as his motto. Easy to state, but difficult to achieve, it has been the central challenge to western philosophical thought ever since. If you don't "understand" yourself, what chance is there of achieving a meaningful existence? Philosophers, spiritual leaders, and self-help gurus have been providing us with guidance ever since on how to reach this enlightened state.

In recent years, the FDA has adopted a new philosophy designed, among other things, to free the pharmaceutical industry from its shackles and stimulate innovation by enhancing and modernizing the regulation of pharmaceutical manufacturing and product quality.[1] The challenge is for the pharmaceutical industry to demonstrate a deep understanding of its processes and the risks involved. Its philosophy for achieving this is perhaps best captured in not one, but two mottos: "Know Thy Process" and "Know Thy Risk."

The first part of this article reviews the drug development process and the methods available for "understanding" a drug manufacturing process. The second part discusses the concept of "risk" and our attitudes toward it. It provides an overview of the methods available for identifying hazards and evaluating the risks to a patient in a drug manufacturing process and discusses the question "when is the risk acceptable?" It advocates the use of Probabilistic Risk Assessment (PRA) in Quality Risk Management (QRM), which is not widely practiced within the industry at present.

Twenty-two years ago the banking industry was deregulated and revitalized, a process that was dubbed, "The Big Bang." The onus was on the banks to assess their risks and manage their business appropriately under the watchful eyes of the regulators. The result has been the near total collapse of the global financial system. Is this new FDA initiative the pharmaceutical industry's Big Bang and will our industry fare better?

## The Drug Discovery and Development Process

The process of drug discovery and drug development is a business, organizational, and regulatory process. Some estimates[28] put the cost of bringing a drug to market at $500 million to more than $2 billion and taking on average 12 to 14 years depending on the therapy or the developing firm; although in special cases, such as drugs to beat AIDS, the FDA has encouraged a fast-track process. The regulators seek to ensure that all drugs brought to market are safe and effective. Why is the drug discovery and development process so expensive and why does it take so long? Well, for every 10,000 New Drug Entities (NDEs) identified during the drug discovery process, about five are considered safe, following pre-clinical evaluations, for testing in human volunteers. Following a further seven years of clinical testing in patients and an 18 month FDA review, only about one NDE out of the five will gain approval as a marketed drug treatment.[26] The development process for new medicines typically proceeds as shown in Table A. There are many excellent sources of detailed information on this process.[3,4,5]

A great deal of effort has been expended in the last few years to streamline regulatory

*Continued on page 26.*


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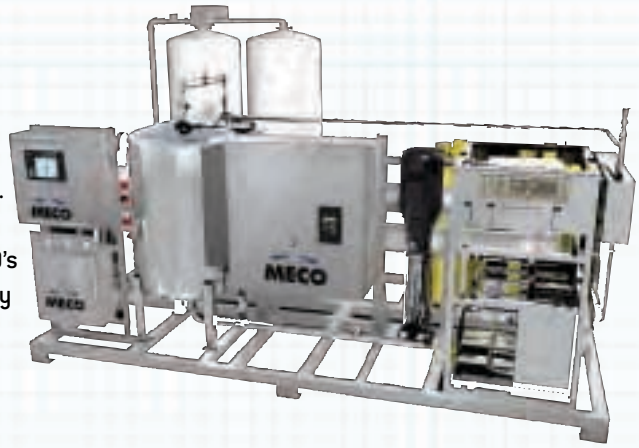


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submissions. If pharmaceutical companies submit their information in a standard format, it should be easier and therefore quicker for the regulators to review it. This should result in less recycle. The culmination of this effort is the Common Technical Document.[6]

In addition to specialists in biology and therapeutic chemistry, the discovery of a new drug involves the collaboration of pharmaceutical R&D specialists and clinical research teams composed of doctors, pharmacists, nurses, chemists, and other health specialists. Efficient information and knowledge management can potentially save valuable years and millions of dollars associated with the drug discovery and development process and a collaborative approach among these professionals can accelerate the process of expediting and approval of new drug entities. Herein lies one of the biggest opportunities to cut costs, but it does require great business vision and leadership.[7]

Another approach to improve efficiency is the recognition that the many steps in the process require different levels of experimentation. The early phase of drug discovery has components of real innovation, components of experimentation, and components that involve set routines. This model of innovation, experimentation, and commoditization ensures new ways to do work are adopted continually and allows disciplines to use appropriate internal and external resources for the right work.[8]

## Taking a Drug into Full-Scale Production

What Table A does not address is the development and scale-up of the laboratory drug manufacturing process to

**Target Identification**
Drugs normally act on cellular or genetic chemicals in the body, known as targets, which are believed to be associated with disease. Research scientists will identify and isolate a target to learn more about its functions and their influence on disease. New Drug Entities (NDEs) are then identified that interact with the target in ways that are helpful in treating a specific disease.

**Target Prioritization/Validation**
Those targets most likely to be useful in the development of new treatments for disease are selected. Tests take place to confirm that interactions with the drug target are associated with a desired change in the behavior of diseased cells and compounds can then be identified that have an effect on the target selected.

**Lead Identification**
Lead compounds or substances are those believed to have potential to treat disease. Scientists compare known substances with new compounds to determine their likelihood of success. Leads are often developed as collections, or libraries, of individual molecules possessing properties needed in a new drug. Testing is done on each molecule to confirm its effect on the drug target.

**Lead Optimization**
Here the properties of various lead compounds are compared in living organisms (in vivo) and in cells in the test tube (in vitro) to see how they are metabolized and affect the body; this allows the pharmaceutical and biotechnology companies to select those compounds with the greatest therapeutic potential.

**Pre-Clinical Technology**
Extensive laboratory development tests are carried out on the investigational drug in living organisms (in vivo) and in cells in the test tube (in vitro).

**Chemistry Manufacturing and Controls (CMC)/Pharmaceutics**
A multi-discipline team take the results of the pre-clinical testing and determine how best to formulate the drug. Regulatory agencies require testing that documents the physicochemical properties - chemical composition, purity, quality, and potency of the active ingredient and of the formulated drug.

**Pharmacology/Toxicology**
Pharmacological testing determines the effects of the investigational drug on the body and toxicology studies identify potential risks to human beings.

**Investigational New Drug Application**
Investigational New Drug (IND) in the US, Clinical Trial Exception (CTX) in the UK, and Clinical Trial Authorization (CTA) (in Australia) are examples of requests submitted to the appropriate regulatory authority for permission to begin clinical testing in humans. The regulators require that all test results are provided with the application for their review.

**Independent Review Board**
In addition to permission from the regulator, an institutional or independent review board or ethical advisory board must approve the test protocol, as well as the consent documents that volunteers sign, prior to participation in a clinical study. This process seeks to ensure that the trial is ethical and the rights of study participants are protected.

**Clinical Studies**
Clinical testing is performed in stages with increasing numbers of patients tested in each successive stage:

***Phase I Clinical Testing***
Typically takes six to nine months. These are the first studies conducted in humans and about 20 to 100 healthy volunteers take the investigational drug for short periods. The objective is to verify the safety and tolerability of the candidate drug in humans.

***Phase II Clinical Testing***
Typically takes from six months up to three years. Testing is conducted on several hundred patients suffering from the condition the investigational drug is designed to treat. The objective is to determine effectiveness and safety in patients.

***Phase III Clinical Testing***
Typically takes between one and four years. Testing is conducted on thousands of patients. The objective is to determine expanded effectiveness and safety in patients.

**New Drug Application**
New Drug Application (NDA) in the US and Marketing Authorization Application (MAA) in the UK are examples of applications submitted to the appropriate regulatory authority for permission to market a new drug. The regulators require that all information collected during the drug development process is provided with the application for their review. The application must present convincing evidence that the drug will have its stated effect when used under the prescribed conditions. The regulatory body may inspect the facilities where the drug will be manufactured. This stage of the approval process can take between six months and two years.

**Additional Clinical Studies**
Before and after the regulator has approved a drug, pharmaceutical companies may conduct additional late stage studies, which can last from several months to several years:

***Phase III Clinical Testing***
Some extended Phase III trials often begin, while the regulatory submission is pending, to provide additional safety data, or test the drug for additional conditions for which it may prove useful. Some companies call these Phase IIIb studies.

Phase IV studies expand the testing of an approved drug to broader patient populations. The long term effectiveness and the cost of the drug compared to alternatives.

**Post Approval Studies**
These studies test a marketed drug on new age groups or patient types or they may investigate previously unexpected side effects or related risk factors.

Table A. The drug approval process.

*Continued on page 28.*

a full-scale production. Figure 1[9] shows in block form the technology transfer process. This is the process of taking the drug substance, the drug product, and the analytical tests and methods from the R&D sites to the commercial manufacturing site. It is in this area where most of the ISPE membership is probably involved.

The cost of getting technology transfer wrong is enormous. A product that is six months late getting to market can lose out on a significant percentage of the estimated profit over the product's lifecycle.

Technology transfer also means transferring all the associated knowledge, information, and skills from R&D to be able to manufacture the drug substance and drug product in full-scale production. In the past, this process has sometimes been problematic and inefficient, due to poor knowledge management. Much of the knowledge gained in early studies was not transferred to the process chemists and process engineers, resulting in delays downstream in getting the production plant commissioned and the process operating and validated.

## Quality by Design

In an attempt to improve this state of affairs the regulators and industry in the International Conference on Harmonization (ICH) process, have adopted the principle of Quality by Design (QbD).[10, 27] This is a means of assuring the quality of a drug as it relates to its safety and efficacy. In practice, this means that the product's Critical Quality Attributes (CQAs) and CQAs of drug substance, excipients, intermediates (in-process materials), and Critical Process Parameters (CPPs) impacting on drug product CQAs should be identified and characterized. The CQAs must be controlled within an appropriate limit, range, or distribution to ensure the desired product quality and a CPP is a process parameter whose variability has an impact on a critical quality attribute; therefore, should be monitored or controlled to ensure the process produces the desired product quality. We need to know by how much we can vary the product formulation, manufacturing operating parameters, and raw material quality and still maintain acceptable product quality. This region of acceptable variability could be represented as a Design Space, which is defined as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Outside of these ranges lies the boundary layer where predictions of product performance are uncertain. With this knowledge, engineers can set control ranges for the critical instruments (i.e., those deemed to impact on CPPs and CQAs) on the plant within which acceptable product quality and performance is assured. It also is necessary to assess the impact of each process step on product quality. This helps minimize the subsequent validation effort of *Continued Process Verification*.[33] To achieve this, we need to explore every detail that might impact on product quality, using sound science, a risk-based approach, and common sense. Effort can then be focused on those areas that have a significant impact.

This more substantial development and process optimization effort, providing greater process understanding based on solid science and risk management, has important business and other benefits.[31] It means that improvements of the process or product that do not affect product quality could potentially be made without post-approval submission to the regulatory body which would otherwise slow the process down considerably.

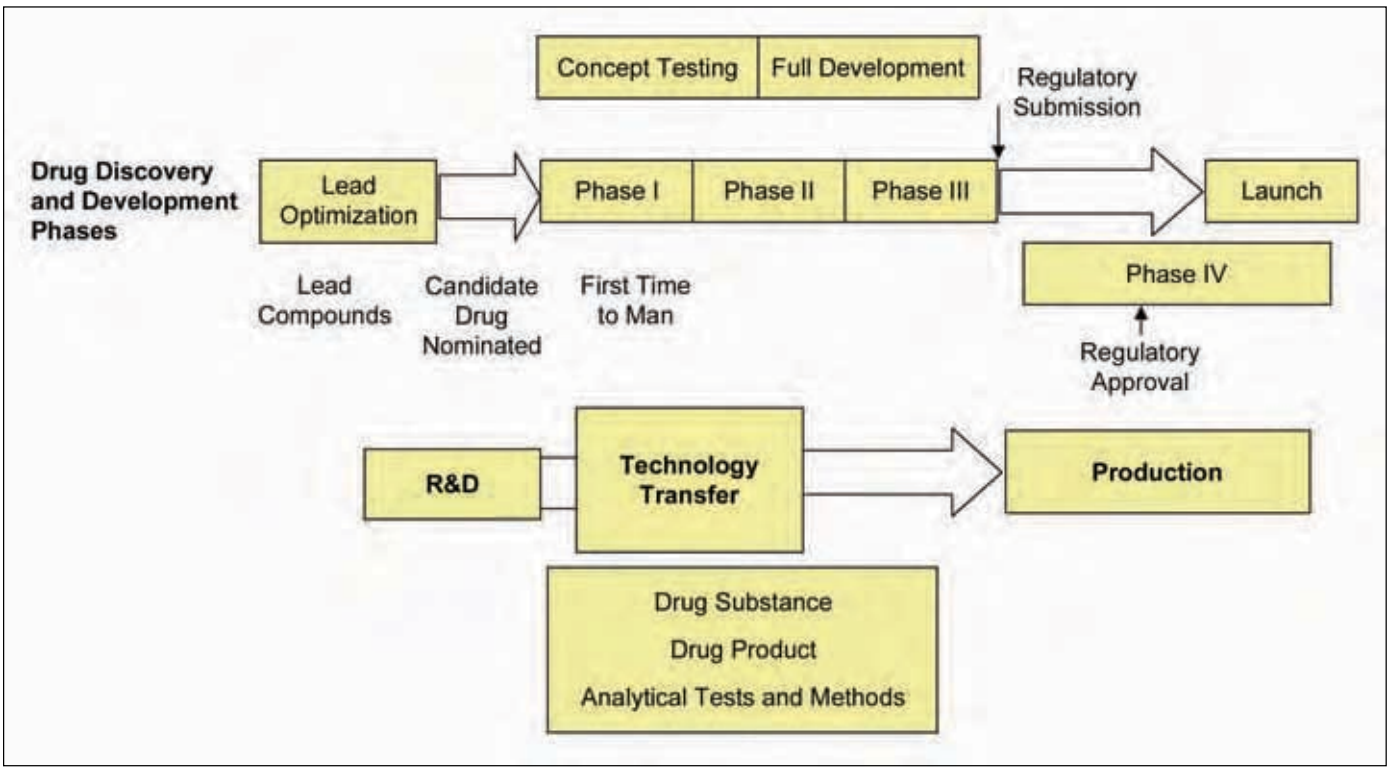


Figure 1. The drug discovery and development process and technology transfer.

*Continued on page 30.*

# **Scale-up –** Lab to Production

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## Lab to production solutions increases efficiency and reduces risk during scale-up

The ability to scale-up liquid injectable filling has become easier with the introduction of the Bosch FLT clinical scale vial filler combined with the PreVAS single-use dosing system.

**Single-use Dosing System**
The PreVAS system offers a cost effective dosing system that can evolve with your product as it goes through clinical trials to production. The flexible design of the dosing system allows expansion without changing dosing principles, technologies, methods, or introducing new product contact parts. This ability to stay with one accurate dosing system from clinical filling to development and through production can greatly reduce validation hurdles and shorten market introduction time.

**PreVAS Advantages**
PreVAS systems are the industries first single-use dosing systems designed to take full advantage of the Rolling diaphragm pump which offers a highly accurate dose over time and has gentle product handling characteristics. PreVAS systems are tailor made to your specifications including all tubing pumps, filling needles fittings and intermediate product bags. Systems are delivered with a prevalidation package, fully assembled, and sterilized for immediate use.

**Lab Scale Vial Filler**
The FLT is a small scale, 30 vial per minute, vial filling system designed to offer features similar to a full scale filling system. The FLT offers a wide variety of options including over gassing, stoppering, capping, barrier systems, and check weighing on one machine reducing labor, risk and product loss. Minimal size parts, simple operation and rapid change over increase versatility.

Together the FLT and the PreVAS are the best package available for product development if time to market, product loss, and scalability are concerns.

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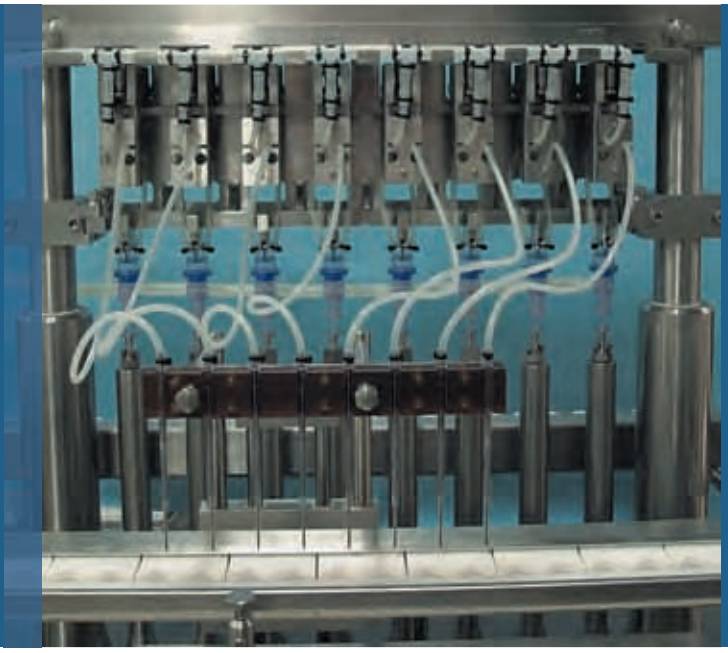

QbD involves thinking ahead ("begin with the end in mind"). It requires a clear roadmap for product development and preparation for technology transfer. It requires more resource to be applied earlier in the drug development phase. It also requires the use of technologies that support better knowledge management to allow us to gather, store, and retrieve knowledge and share it within teams and across our organizations so that it can be fully utilized in the continuous improvement of our products and processes. This would help to eliminate the need to over-design facilities and would enable focused risk-based verification of suitability and fitness for purpose of the process plant.

## PQLI

The ISPE Product Quality Lifecycle Implementation (PQLI) initiative was launched in June 2007[29] to help industry find practical approaches to the global implementation of recent quality guidelines published by the International Conference on Harmonization (ICH),[11,22,30] which includes an understanding of QbD principles.

## Understanding the Process

Some of the major advanced methodologies and technologies that can help to achieve a comprehensive process understanding are discussed below and references are given to more detailed sources of information. Large pharmaceutical majors have most of these methodologies and technologies in-house, but smaller pharmaceutical companies can now access these through specialist organizations.[11]

**Design of Experiment (DoE)** is a method used to determine the relationship between the different factors affecting a process and the output of that process. This method was first developed in the 1920s and 1930s by Sir Ronald A. Fisher. With the advent of modern desktop computing power, sophisticated software packages, and expert consultancies, these techniques are now available to every company.

Experimental design can be applied whenever we need to investigate a phenomenon in order to gain understanding of, or improve, performance.

To build a design we carefully choose a small series of experiments that are to be performed under controlled conditions. There are four interrelated steps in building a design.[12]

1. Define an objective to the investigation, e.g., "better understand" or "sort out important variables" or "find optimum."
2. Define the variables that will be controlled during the experiment (design variables) and their levels or ranges of variation.
3. Define the variables that will be measured to describe the outcome of the experimental runs (response variables) and examine their precision.
4. Among the available standard designs, choose the one that is compatible with the objective, number of design variables and precision of measurements, and has a reasonable cost.

Standard designs are well-known classes of experimental designs. They can be generated automatically as soon as we have decided on the objective, the number and nature of design variables, the nature of the responses, and the number of experimental runs we can afford. Generating such a design will provide us with a list of all experiments we must perform, to gather enough information for our purposes.

DoE is widely used in research and development, where a large proportion of the resources go toward solving optimization problems. The key to minimizing optimization costs is to conduct as few experiments as possible. DoE requires only a small set of experiments and thus helps to reduce costs.

Areas where DoE is used in industrial research, development, and production include:

- optimization of manufacturing processes
- optimization of analytical instruments
- screening and identification of important factors
- robustness testing of methods
- robustness testing of products
- formulation experiments

**Multivariate Data Analysis (MVA)** refers to any statistical technique used to analyze data that arises from more than one variable. This essentially models reality where each situation, product, or decision involves more than a single variable. The information age has resulted in masses of data and the ability to obtain a clear picture of what is going on and make intelligent decisions is a challenge. When available information is stored in database tables containing rows and columns, MVA can be used to process the information in a meaningful fashion. With MVA, we can:

1. Obtain a summary or an overview of a table. This analysis is often called Principal Components Analysis or Factor Analysis. In this overview, it is possible to identify the dominant patterns in the data, such as groups, outliers, trends, and so on.
2. Analyze groups in the table, how these groups differ, and to which group individual table rows belong. This type of analysis is called Classification and Discriminant Analysis.
3. Find relationships between columns in data tables, for instance relationships between process operation conditions and product quality. The objective is to use one set of variables (columns) to predict another, for the purpose of optimization, and to find out which columns are important in the relationship. The corresponding analysis is called Multiple Regression Analysis or Partial Least Squares (PLS), depending on the size of the data table.

**Process Analytical Technology (PAT)**[13] is an approach that is intended to support innovation and efficiency throughout the product lifecycle. It consists of a set of tools and principles (including MVA) for understanding and controlling the manufacturing process. It can be used to define the CPPs, which as mentioned above, are those process variables which need to be controlled to maintain the CQAs. The power of this tool is that it is possible to:

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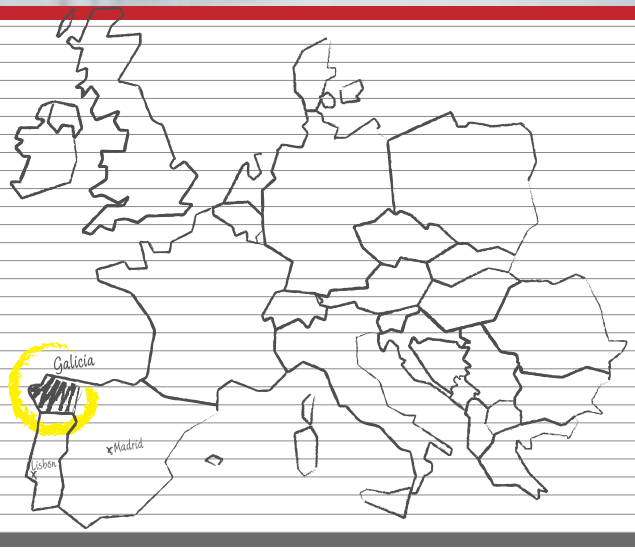


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- Help determine a parameter or attribute which contributes to "real time release testing"; the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.
- Monitor some parameters on line or at line.
- Conduct sensitivity analyses to determine the impact of process deviations on the product's CQAs.
- Monitor and control the process endpoint and for continuous improvement.
- Generate mathematical relationships promoting process understanding.
- Enable real-time monitoring and ultimately, real-time release.

PAT can be applied effectively to batch processes, but the greatest benefits are obtained when it is utilized with continuous processes, which are finally starting to make inroads into pharmaceutical production.[14]

**Process Modeling** "is the art or activity of building a mathematical model of the process (or a product, for that matter) by describing its fundamental physical and chemical relationships – without specifying how they are to be solved."[15]

Groundbreaking general purpose process modeling tools now allow a highly accurate model of a chemical process to be built. With such a process model, it is possible to perform all the activities required to model across the process lifecycle, from conceptual design and laboratory experimentation through detailed engineering design to operation. We can:

- **Perform simulation runs** (steady state and dynamic) to see what happens if feed conditions are varied.
- **Estimate parameters** using model-based data analysis and validation techniques and comparing these against experimental data. This can enhance predictive accuracy significantly and provides information that can be used in formal risk analysis.
- **Design experiments** to refine the parameter estimations and reduce the risk associated with measurement inaccuracy.
- **Perform optimizations** – dynamic or steady-state – on the model, to directly calculate optimal trajectories or values rather than undertaking lengthy trial-and-error investigations.
- **Generate linearized models** for use in control design applications or Model-based Predictive Control (MPC), gain scheduling or any other activity that requires linear models.
- Because this is a model and not a simulation, **simulate "backward"** to find out what feed or unit values give rise to the desired product qualities, at no additional cost in terms of execution time or complexity of model.
- **Generate an Equation-Set Object (ESO)** for other software – for example, plant-wide optimizers – to use.

By way of example, **Process Control** of bioreactors is difficult, due to their non-linear dynamic behavior and the fact that the model parameters vary in an unpredictable manner. This complexity inhibits accurate modeling. The lack of suitable sensors makes the process state difficult to characterize, but continuous processing is desired in order to optimize throughput. There are a number of techniques available for the non-linear control of processes, e.g., differential geometric approach, reference synthesis technique, predictive control design, etc., but their major disadvantage is the computational time required to perform the prediction optimization. Recently, researchers using a nonlinear controller,[16] based on a polynomial discrete time model (NARMAX), have extended its use to fermenters and report satisfactory results.

**Britest**[17] is a not for profit company directed by its members; a consortium of manufacturing companies (including pharma), major engineering contractors, and top universities. The aim of Britest is to improve processes, both chemical and physical, from conception to operation; to apply effort where it will give most benefit; to leverage existing knowledge to maximum effect; to identify important gaps in our knowledge and produce a targeted program of experimentation.

This is achieved using the Britest Toolbox, a set of tools to help groups structure their thinking. This works alongside other tools, such as DoE, etc. Most tools tend to be used by a team with a facilitator guiding the group as follows:

1. Start with an overview of the business case.
2. Review the whole process.
3. Identify where most benefit is to be gained.
4. Analyze those areas in detail.
5. Find where data is missing/not well understood.
6. Experiment/research to obtain missing data.
7. Include data in the analysis and complete the model.
8. Use the model to underpin decision making.

It is all about knowledge management. In order to achieve true process understanding, many disciplines are involved. Bringing these disciplines round a table in interactive discussion, pooling knowledge, and facilitating group conceptualization is what Britest is about. It is an effective tool for QbD. Britest's process understanding development philosophy is shown in Figure 2.

**Visual Literacy**[18] is the ability to evaluate, apply, or create conceptual visual representations for communicating new knowledge and devising new ways of representing insights. There are some wonderful tools at the Visual Literacy Web site, including a Periodic Table of Visualization Methods.[19] This is a compilation of 100 existing visualization methods compiled using the logic, look, and use of the periodic table of the elements. As they say, a picture paints a thousand words!

**Modeling and Decision Support Tools.** A useful Web site that refers to many useful tools that can be employed in the service of process understanding is courtesy of the Institute for Manufacturing at the UK's Cambridge University,[20] which lists them alphabetically and also under the headings of: Information Control, Paradigm Models, Simulation Models, Ways of Choosing, Representation Aids, and Processes.

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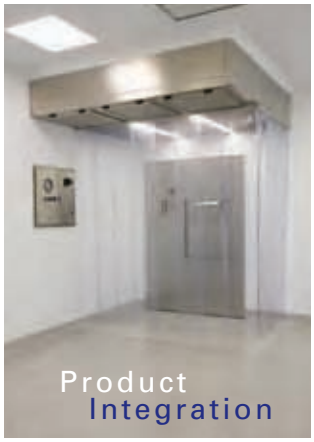



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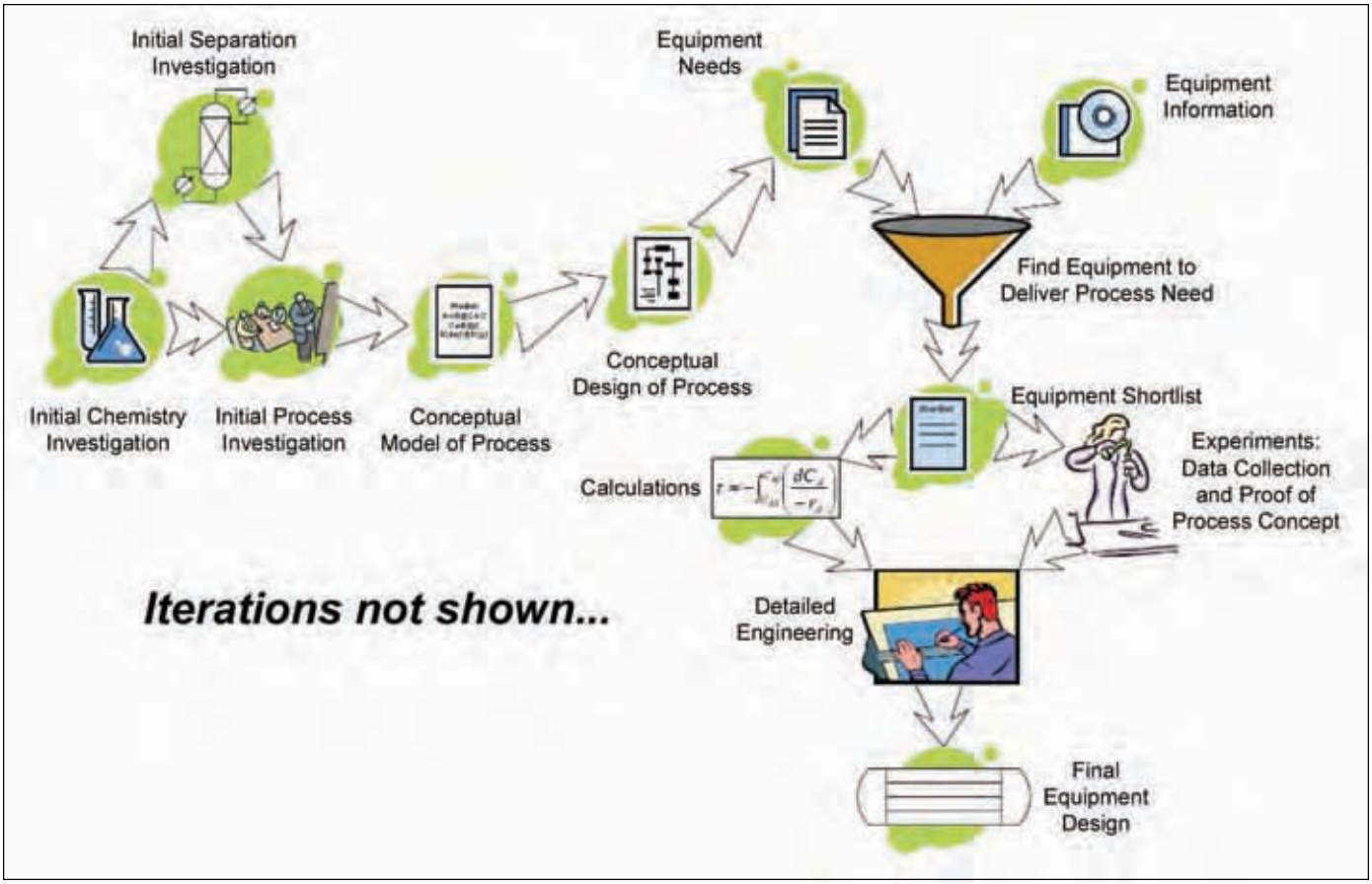


Figure 2. Process understanding development philosophy.

The above discussion has highlighted the many tools available for understanding our processes. The technological landscape has never been more exciting; technology and new techniques are developing rapidly and there has never been a better time to "Know Thy Process."

## Introduction to Risk Management

The latest FDA philosophy advocates a risk-based approach to, among other things, "encourage the early adoptions of new technological advances by the pharmaceutical industry."[1]

Whether we like it or not we are all gamblers in the game of life. From the moment of conception, we are exposed to hazards; from nature, from the environment, from other people, from other creatures, and from ourselves and our creations. We have absolutely no control over some hazards: some we can totally control. However, in many cases, hazards can be mitigated, but not completely removed.

Risk management is important for us all as individuals and for our organizations. In the old days, when life was not so busy, we did not dwell too much on unhappy possibilities. Fire and crossing roads were perceived to be significant hazards and we were taught to take sensible precautions. There was not so much forward thinking, and in due course, accidents would happen, lessons would be learned, and we would start again with a revised set of precautions in place.

The rapid pace of change in the development of drugs, technology, and communications has led to organizations undertaking increasingly complex and ambitious projects. This complexity and the change of pace require a very formal forward-looking approach to risk management. The recent problems with Heparin[21] have clearly demonstrated that in complex supply chains, there is uncertainty, lack of knowledge, and the potential for rare, high-consequence outcomes. The good thing for the life sciences industry as far as risk management is concerned is that all the hard work has been done by other industries, namely, aerospace, nuclear, and the hydrocarbons industry. They have come up with sophisticated techniques to manage their risk. The challenge is how to take this knowledge on board and apply it to our own system of Quality Risk Management as defined in the guidance for industry, ICH Q9, which has been adopted by the FDA and the EU.[22]

We must have some means of estimating the probability of failure of the elements of drug manufacturing systems to allow a manufacturer to focus attention and limited resources as effectively as possible on the most critical systems.

Risk management involves:

1. Identification of the risks.
2. Evaluation of the risks.
3. Control of the risks.
4. Financing the decisions.

In this article, we are focusing on Identification and Evaluation of the risks.

## Risk Assessment Techniques

The latest, most sophisticated technique available for risk assessment is **Probabilistic Risk Assessment (PRA)**, which was once deemed too "difficult," but has now reached a mature stage in its development. This technique is not widely used in the pharmaceutical industry at present, but there is an awareness that it may be useful in the design of complex pharmaceutical molecules, such as monoclonal antibodies.[2]

Sometimes risk is defined as the expected value of an undesirable consequence. However, this is only a summary measure and a probability distribution for the consequence affords a much more detailed description of risk. Determining risk generally involves answering the following questions:

1. What can go wrong?
2. How likely is it?
3. What are the consequences?

The answer to the first question is a set of accident scenarios. To answer the second question we need the probabilities of the scenarios and for the third an estimate of their consequences. This definition emphasizes the development of the accident scenarios and makes them a part of the definition of risk. The scenarios are one of the most important results of the risk assessment.

PRA begins with a set of "Initiating Events" (IEs), which impact the system, causing it to change its operating state or configuration. For each IE, the analysis proceeds by determining the additional failures that may lead to undesirable consequences. Then the consequences of the scenarios are determined, as well as their frequencies, and finally they are put together to create a risk profile of the system, which supports risk management. Figure 3, borrowed from NASA, shows the implementation of these concepts in PRA.[23]

PRA studies often require special analysis tools, such as Human Reliability Analysis (HRA) and Common Cause Failure (CCF) analysis. HRA deals with methods for modeling human error (which are deemed to be the largest contributors to sterility failure in aseptic processing). CCF deals with methods for evaluating the effect of inter-system and intra-system dependencies, which tend to cause simultaneous failures and thus significant increases in overall risk.

PRA studies should be performed:

- when information is not sufficient to comprehensively assess strengths and weaknesses of complex systems by other means
- when important complex jobs must be performed successfully for the first time
- in all lifecycle phases of a complex system

An integrated PRA has its own value that is greater than the sum of its parts. Some of the benefits of an integrated PRA are:

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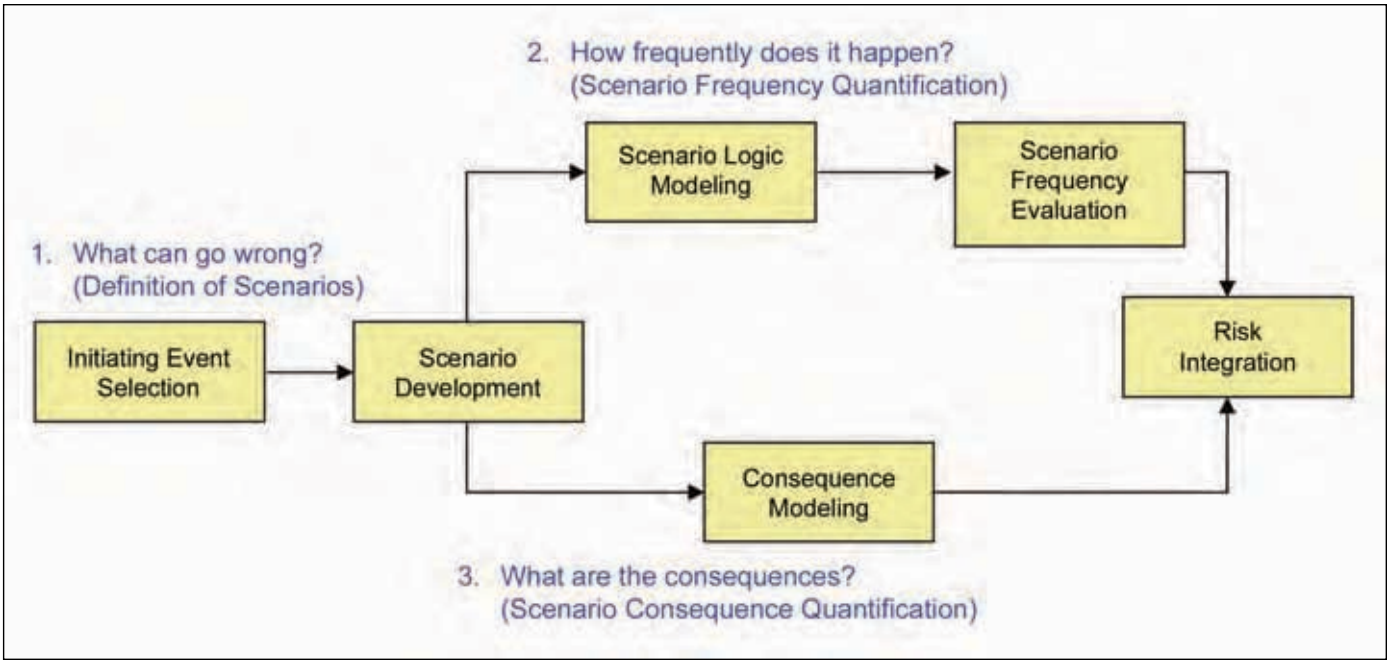


Figure 3. Implementation of risk assessment using PRA.

- The model configuration can be kept aligned with the system configuration.
- Facilitates "what if?" analyses for proposed design changes and upgrades.
- Provides basis for risk-based maintenance.
- Provides basis for risk-based decision-making.
- Captures the knowledge of experts.

Some of the benefits of the numerical results of PRA are:

- Enables us to respond to those who demand "give me the numbers."
- Allow us to express the uncertainty in our state of knowledge – a gap analysis.
- Comparison of risks with risks "acceptable" to society.
- Provide relative ranking of "risk drivers" and show where to concentrate our limited resources for maximum risk reduction.

To make comparisons of the risks of different activities, risk analysts use the term micromort, which is a one-in-a-million chance of dying. According to the United Kingdom Rail Safety and Standards Board, the average person experiences a micromort by:

- driving 230 miles in a car
- riding six miles on a motorbike
- traveling 6,000 miles in a train
- taking three flights

So what about the traditional methods of risk assessment?

Failure Modes and Effects Analysis (FMEA) and Hazard Analysis are useful as inputs to a PRA, but do not meet the full requirements of the PRA as they do not take account of dependencies and multiple failures. They only show worst case consequences and so cannot provide total probabilities of end states with uncertainties. Hazard analyses, if available, are useful as inputs for identifying initiating events and scenarios and FMEAs are useful in checking Fault Tree basic events. Interface FMEAs are useful in checking functions that need to occur for system success. If FMEAs or Hazard Analyses are not available, a PRA will substitute for them because all the information will be there, albeit in a different form, providing the analysis is complete. PRAs are essentially linked Fault Trees. If appropriate, portions of a Fault Tree Analysis (FTA) can be used as part of the PRA, but it is difficult to split the PRA into many different trees with different top events and qualitative Fault Trees are very different to quantitative ones. Fault Trees do not show time or sequences. In summary, the FTA supports the PRA, not vice versa.[24]

While the mathematics can become complicated, PRA software is available to speed up the process. The two most well-known examples are:

- Quantitative Risk Assessment System (QRAS) – developed for NASA by the University of Maryland.
- Systems Analysis Program for Hands on Integrated Reliability Evaluations (SAPHIRE) – developed for the US Nuclear Regulating Commission.

It is said that during the early Apollo project the question was asked about the probability of successfully sending astronauts to the moon and returning them safely to Earth. Some sort of risk calculation was performed and the result was 0.2, a very low probability of success. This discouraged NASA from performing quantitative risk analysis. NASA pushed on regardless and five successful moon missions out of six attempts did not imply any need for PRA. Instead,

NASA relied on FMEA for system safety assessments, which continue to be a requirement by NASA to date in all its safety related projects.

On 28 January 1986, after 25 successful flights, the Space Shuttle Challenger exploded. The resulting investigation by the US House of Representatives, concluded: "Without some means of estimating the probability of failure of the various [shuttle] elements it is not clear how NASA can focus on the most critical systems." Later the Slay committee said: "The committee recommends that probabilistic risk assessment approaches be applied to the shuttle risk management program at the earliest possible date. Databases derived from Space Transportation System (STS) failures, anomalies and flight test results, and the associated analysis techniques, should be systematically expanded to support probabilistic risk assessment, trend analysis, and other quantitative analyses relating to reliability and safety."

Since then, NASA has developed the PRA technique extensively and uses it on all its safety projects.

Figure 4 is borrowed from NASA[23] and shows the relationship between risk management, PRA, and the traditional risk assessment techniques.

In 2008, the results of a survey of quality risk management practices in the pharmaceutical, devices, and biotechnology industries were published.[25] Among the major findings are:

- The "aseptic processing/filling" operation is the functional area identified as having the greatest need for risk assessment and quality risk management.
- The most widely used methodology in industry to identify risk is FMEA. This tool was most widely applied in assessing change control and for adverse event, complaint, or failure investigations.
- Despite the fact that personnel training was identified as the strategy most used for controlling/minimizing risk, the largest contributors to sterility failure in operations are still "personnel."
- A majority of correspondents verified that they did not periodically assess their risk management programs.
- A majority of the correspondents desired to see case studies or examples of risk analysis implementations (as applicable to aseptic processing).

FMEA is a very good technique that is easy to understand and use. We should continue to use it as it is valuable for assessments carried out at component level and also is very useful in capturing knowledge. However, it will not show the "big picture" and it cannot deal with system interactions and human error in the way that PRA can.

Establishing quality risk management within the corporate culture is not easy. It must be driven by the CEO. There are subject matter experts out there with the knowledge and experience to help.

It is important to note that risk assessments rest on estimating probabilities, which is notoriously difficult. Many court rulings relating to cot deaths, DNA matches, etc., have had to be overturned on appeal, highlighting the inherent difficulty with probability-based statistical evidence provided by expert witnesses.[32]

## Summary

We are very well placed to understand our processes – better than at any other time in history. We may be able to identify all the modes of failure of our processes, but evaluation of

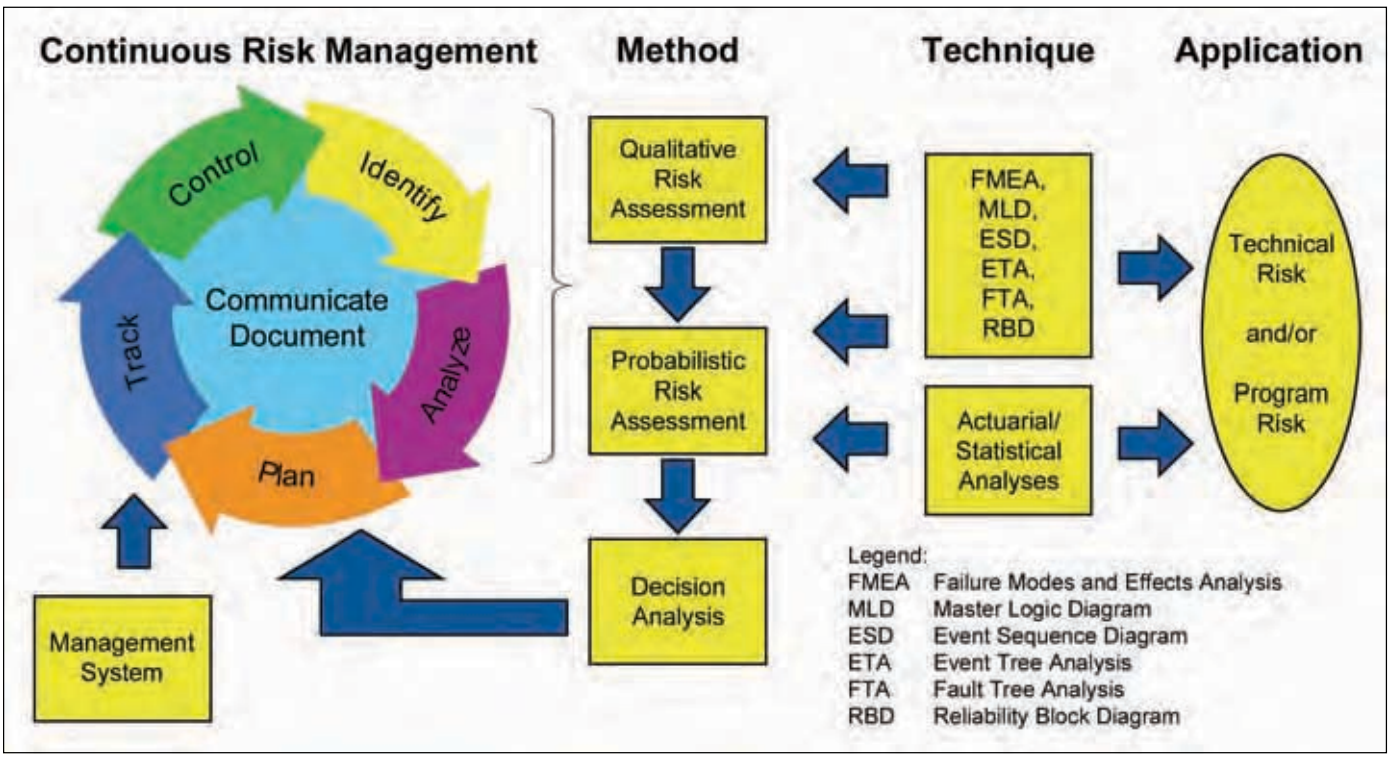


Figure 4. Relationship between risk management and Probabilistic Risk Assessment (PRA).

*Concludes on page 38.*

the risks depends on our ability to accurately assess the probabilities of failure and this is difficult. Other regulated industries, like the nuclear and aerospace industries, have suffered severe mishaps in their development, but now have mature risk management cultures. Others, most notably the financial and banking industry, have tried to manage their risk, but have been confounded by the complexity of their systems and have been brought to the brink of collapse. The pharmaceutical industry must tread cautiously and learn from the successes and failures of others.

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## About the Author

**Robert Jones** is a chemical engineer with more than 30 years of industrial experience. He is a Corporate Quality Assurance Engineer in the Health, Safety, Environment, Quality, and Security (HSEQS) Management Group at Foster Wheeler Energy Limited, the global engineering, procurement and construction contractor in the United Kingdom. Jones previously spent 18 years in Foster Wheeler's Pharmaceutical Division, where his experience encompassed design, GMP compliance, and validation of API, secondary, bulk sterile, and biotech facilities. He can be contacted by email: robert_jones@fwuk.fwc.com.

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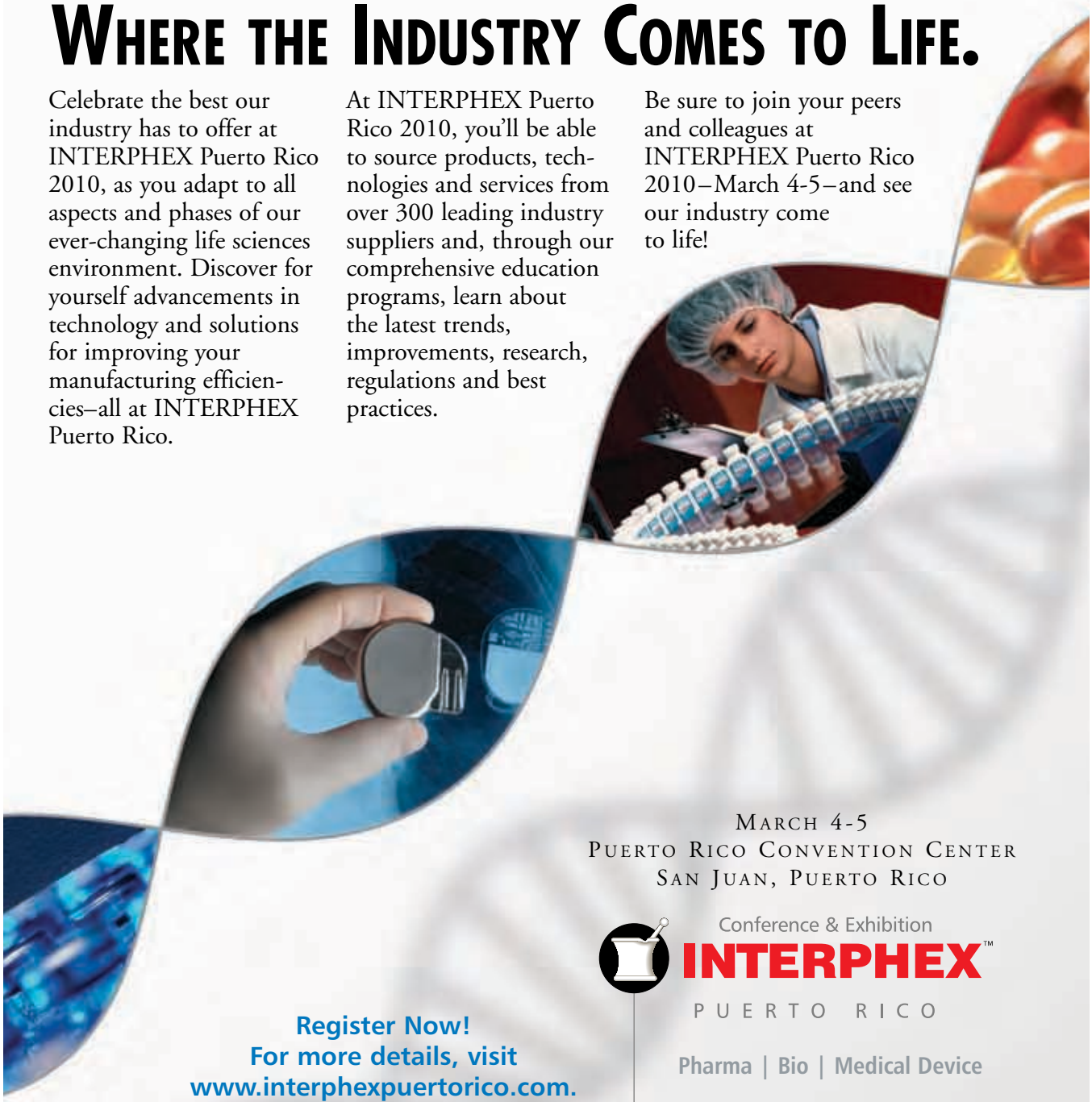

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**Jon Clark and Cliff Campbell discuss the findings of a project to determine a regulatory approach for a firm to change the manufacturing site for sterile drug products without requiring manufacturing data before approval.**

# PHARMACEUTICAL ENGINEERING Interviews

## Jon Clark, Associate Director for Policy, CDER Office of Pharmaceutical Science (OPS), FDA, and Cliff Campbell, CEO, Campbell Informatics

**Jon Clark** is an Associate Director for Policy, Center for Drug Evaluation and Research (CDER), US FDA. After 12 years of experience working in industry, Clark joined the Agency in 1992. He develops guidance documents, is a policy expert, contracts strategic research programs, and manages the environmental assessment review and the compendial operations. Clark is engaged in the Pharmaceutical Quality CGMPs for the 21st Century program, Critical Path Initiative, the Product Quality Research Institute (PQRI), and the International Conference on Harmonization (ICH). From 1980 to 1992, he was employed as an organic synthesis research chemist, first at Beecham Laboratories then at Schering Plough Research, producing various chemical processes, publications, and patents. Clark received his BS in chemistry at the University of Michigan in 1980 and his MS in chemistry at Rutgers University in 1987.

**Cliff Campbell** was educated at University College Cork, and is founder and CEO of Campbell Informatics, a company that provides knowledge management frameworks and consultancy to life-science manufacturers on an international basis. He has been an advocate of intrinsic quality and modular compliance for many years, promoting a back-to-basics approach to the itemization, characterization, and verification of systems and processes across their CMC, QbD and C&Q lifecycles. Campbell is a recognized driver of 21st Century Compliance and was appointed consultant to the FDA's Office of Pharmaceutical Science (OPS) in mid-2008, leading a 12-month assignment on Assessing Risks of Changing Sterile Drug Manufacturing Sites.

**Q** What was the assignment's official title?

**Clark:** Assessing Risks of Changing Sterile Drug Manufacturing Sites.

**Q** What was the underlying objective?

**Clark:** We wanted to explore different regulatory approaches for a firm to change manufacturing sites without requiring manufacturing data before approval.

**Campbell:** The assignment was targeted at sterile manufacturing, both synthetic and biotech, with the core objective as follows: to demonstrate that the risks associated with changing (i.e., relocating or expanding) the manufacturing site for sterile drug products (from formulation to fill) can be managed strictly within the manufacturer's change control process so that a supplement to an application is not required.

**Q** Can you provide some additional background from an Agency perspective?

**Clark:** Yes. It is seen as unnecessarily cumbersome to require manufacturing data in order to confirm criteria that are well established by other means.

*Continued on page 42.*

# Pharmaceutical Processing Systems

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**Campbell:** From an OPS perspective, changing sterile drug product manufacturing sites is considered a major change, requiring applicants to submit a supplement to their applications. OPS has embraced QbD as a means of ensuring that risks associated with manufacturing changes – which still remain major – can be managed within the manufacturer's change control process and as part of current Good Manufacturing Practices (cGMPs). The authorization to do this would be granted through Agency approval of the applicant's Risk Management Plan.

**Q** What type of risks were you mainly concerned with?

**Clark:** Sources of variability and sources of impurity – and the risk of not meeting the requirement for sterility.

**Campbell:** Specifically, sterility assurance failures due to variations in facility, manufacturing process, design space, and/or process control strategies (e.g., validation, sampling, monitoring, and acceptance criteria), and the introduction of impurities to a drug product as a result of changes, raw materials, equipment, and/or container closure components.

**Q** Can you summarize deliverables, schedule etc?

**Campbell:** The assignment ran from July 2008 to June 2009 with the following deliverables:

| | |
|---|---|
| • Work Plan | 2 months |
| • Synthetic Drug: | |
| Interview Summaries | 3 months |
| Final Report | 2 months |
| • Biotech Drug: | |
| Interview Summaries | 3 months |
| Final Report | 2 months |

**Q** Can you tell us which companies participated in the interview process?

**Campbell:** Allergan, Amgen, Genentech, GSK, Genzyme, Pfizer, Solvay, Wyeth.

The National Institute for Pharmaceutical Technology and Education (NIPTE) in the US and University College Cork in Ireland also contributed from an educational perspective.

**Q** Was the assignment conducted as part of a Cooperative Research and Development Agreement (CRADA) or was some other format applied?

**Clark:** The assignment was performed as a research contract. The concept was published as a Request for Proposal (RFP) and was open to all bidders. The FDA will own the reports that are produced.

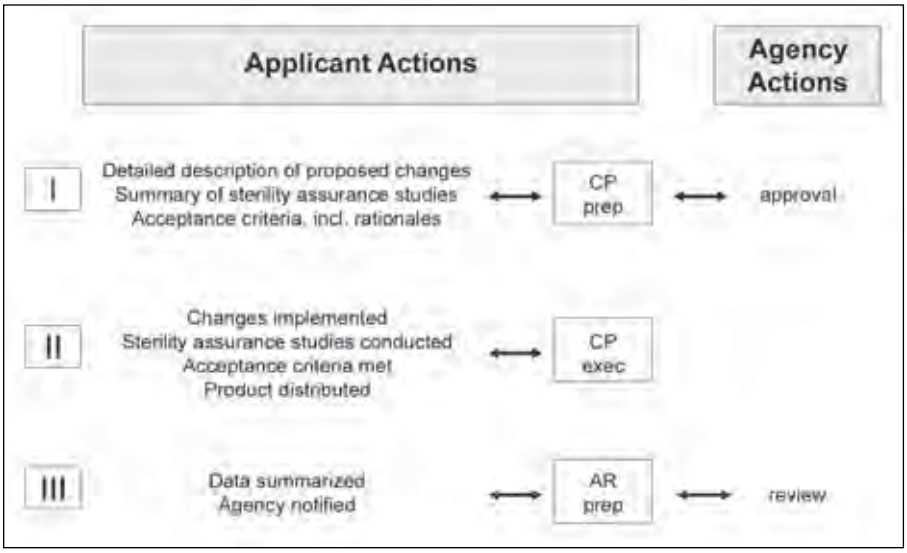


Figure 1. Summary of applicant and agency actions.

**Q** Can you describe the interview process and how the interviews were documented?

**Clark:** The FDA required that Office of Management and Budget (OMB) requirements for this kind of survey work be followed. We also allowed for the contributing parties to remain anonymous.

**Campbell:** Based on the assignment scope, the following topics were included within the interview process:

- Facility/Equipment
- Environment
- Raw Materials
- Process/Controls
- Components/Closures
- Personnel

In line with the agreed scope of work, synthetic product interviews focused on Terminal Sterilization (TS) and biotech products on Aseptic Processing (AP). Existing FDA guidance in regard to these two areas was examined relative to the above topics and selectively converted into abbreviated checklist form, separate checklists being compiled for TS and AP. Once approved by OPS, these were used to drive the interview sessions, these being conducted in workshop format at individual participant sites. The above process was not a survey, the intent being that the checklists would kick-start a general discussion in regard to the topic in question. In addition to the checklists, several participants provided additional material in support of their chosen approach. The interview sessions were individually documented, the write-ups being previewed by the relevant firm before being presented to OPS.

**Q** Can you describe the final reports and how these were documented?

**Clark:** These were documented as fictional case study submissions to the Agency with the purpose of changing manufacturing sites.

**Campbell:** The contract requirement

was that the reports be written as Risk Management Plans. In summary, the preferred Agency format was a Comparability Protocol, based on FDA's MAPP 5040.1 Policy (Product Quality Microbiology Information in the Common Technical Document – Quality). This would provide product quality microbiology reviewers with a familiar format, and one that could be mapped to an applicant's original application if required.

**Q** What were the major findings?

**Clark:** The main finding was that the use of a change protocol under 21 CFR 314.70(e) was a feasible approach. This makes implementation easier since some reviews have already been done this way.

**Campbell:** The first key finding is that, properly written, the Risk Management Plan and the Comparability Protocol are the same document, and that these in turn are identical to the traditional Prior Approval Supplement, minus the executed data, which is referenced in summary format in Annual Report. This is shown schematically in Figure 1.

The second finding again relates to comparability, and is a corollary to the above. In many interviews, what was presented in support of inter-site comparability was a gap analysis, which concentrated primarily on the physical or plant layer. What emerged in the course of the assignment is that if Site A and Site B are independently assessed relative to their 'mother spec' (MAPP 5040.1 etc.) then line-by-line comparisons between the two sites are no longer required, comparability becoming an inferred process.

**Q** Where does Failure Mode and Effects Analysis (FMEA) fit in to all of this, and what are the implications, if any, for risk-based C&Q?

**Clark:** FMEA is one of a number of techniques that could be used as a way to organize the information in a coherent way. For example, a firm could use the existing Common Technical Document format and embed FMEA approaches within a protocol this way.

**Campbell:** C&Q was addressed as a standard topic within the Facility and Equipment section of the interviews. From the point of view of current practice, most participants use ISPE's system and component impact assessment process to prioritize and manage their C&Q protocol preparation efforts, even though there is some variation in the extent to which leveraging is applied. A minority of firms are examining ASTM E2500 either as an alternative or as a complement to ISPE. The key issue from a qualification point of view is that, regardless of which qualification model is being used, the commit-

*Concludes on page 44.*


Figure 2. MAPP 5040.1.

ments contained within MAPP 5040.1, etc., are fundamental, and cannot be abbreviated or sidestepped based on risk-assessment.

**Q** Were there any significant differences in findings between Synthetic and Biotech?

**Clark:** Other than the differences between the two technologies, no regulatory differences are expected.

**Campbell:** The two sets of interviews were conducted independently, but commonality quickly became apparent, perceived differences between the product types soon disappearing. In both cases, there was general awareness by participants of the existence, rather than line–by-line content, of prevailing regulations. In many cases, the level of documentation that was presented in support of a particular task or work-practice was probably excessive. The best example of this was the absence of big-picture process flow diagrams capturing process steps, critical quality attributes, critical parameters, in-process controls, static and dynamic environmental monitoring, human interventions, and holding periods.

**Q** Was the topic of outsourcing and contract manufacturing addressed?

**Clark:** Yes. Other than the expected impact that contract manufacturing has on the existing framework, nothing new is expected with the advanced approach that we are proposing.

**Campbell:** Outsourcing was a cause of some concern to OPS, but participant response was consistent and unequivocal: outsourcing is non-contentious as long as it accompanied by the appropriate level of GMP audit and the necessary Quality Agreements are in place between the contract giver and contract receiver.

**Q** How does the assignment integrate with similar initiatives by other groups [e.g., Product Quality Lifecycle Implementation (PQLI), Product Quality Research Institute (PQRI), PDA, etc.]?

**Clark:** The question is too broad to answer. We have found no conflict with these other initiatives, but these deal primarily with specifics, whereas we were more interested in framework.

**Q** How will the assignment's findings be documented and disseminated?

**Clark:** Public workshops and publications will be used to disseminate the information.

**Campbell:** The information will be disseminated by interviews such as this, by white paper(s), and presentations at society annual meetings, etc. Note that the specific interview summaries are not being circulated, due primarilyto the issue of confidentiality. However, the real benefit of the assignment is not so much in the fine detail, but in the general findings relating to criticality and comparability.

**Q** Are FDA's other divisions (OC, ORA, ONDQA) on board or is this a standalone OPS initiative?

**Clark:** This initiative was championed by OPS and involved the review microbiologists for new drugs.

**Q** Was the assignment actual or hypothetical, and what level of regulatory flexibility is available to industry in the here and now?

**Clark:** The assignment was hypothetical, but the regulatory approach that was described is available immediately since it does not conflict with existing regulation or recommendations.

**Q** Will the findings become the basis of an Agency guidance or policy?

**Clark:** It is possible to be expressed as a guidance document for industry or become policy. However, the existing regulation is adequate for this use.

**Q** Is the Agency considering expanding this initiative to include API processes?

**Clark:** It is possible to expand this concept into other areas, but the initiative needs to come from within those groups.

**Q** A final question... what's in it for industry?

**Clark:** The potential to provide a basis for site change criteria that are traceable to the patient and do not require manufacturing data before approval.

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# Good Weighing Practices for the Pharmaceutical Industry – Risk-Based Qualification and Life Cycle Management of Weighing Systems

by Arthur Reichmuth and Dr. Klaus Fritsch

**This article presents a universal method to select and test weighing instruments based on an integrated qualification approach. Considering primarily the user's weighing requirements and risks, it describes a state-of-the-art strategy to ensure reliable weighing processes embedded in any current quality management system.**

## Introduction

Weighing is only the first step of a whole analysis chain in drug discovery and quality control. The quality of weighing strongly influences the quality of the end result so that the US Pharmacopeia specifically requires highly accurate weighing results for assay.[1,2] Good Weighing Practices[3] provide a scientific methodology to selecting and testing weighing instruments within an integrated qualification approach. Based primarily on the user's weighing requirements and prevailing weighing risks, they provide a state-of-the-art strategy to reduce measurement errors and to ensure reliable weighing results. The understanding of weighing process requirements and important balance properties as minimum weight is essential to select an appropriate weighing system in the framework of the design qualification. The performance qualification takes into account these requirements and risks to establish a specific routine testing scenario for the instrument. The higher the risk in case of malfunctioning, and the more stringent the weighing accuracy requirements are, the more frequent balance tests have to be carried out. However, for less risky and stringent applications, testing efforts can be reduced accordingly. Risk- and life cycle management form an integrated part of the overall strategy of Good Weighing Practices to bridge the gap between regulatory compliance, process quality, and cost consciousness.

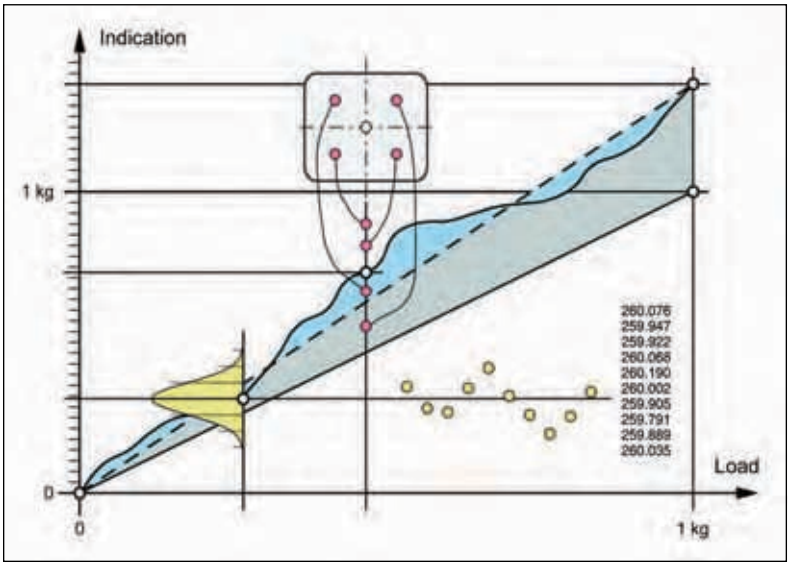


Figure 1. Balance properties: the dashed line with the associated gray area represents the sensitivity offset of the balance, superimposed is the nonlinearity (blue area, indicating the deviation of the characteristic curve from the straight line). The red circles represent the measurement values caused by eccentric loading, and the yellow circles represent the distribution of the measurement values, due to repeatability.

## Selecting a Weighing Instrument

### *Specifications and Uncertainty*

"I want to buy an analytical balance with a readability of 0.1 mg, because that is the accuracy I need for my application."

Statements like this are often heard when establishing a design qualification. In the wake of this requirement, a user may select an analytical balance with a capacity of 200 g and a readability of 0.1 mg, because it is believed that this balance is "accurate to 0.1 mg." This is a misconception for the simple reason that the readability of an instrument is not equivalent to its weighing accuracy.

*Continued on page 48.*

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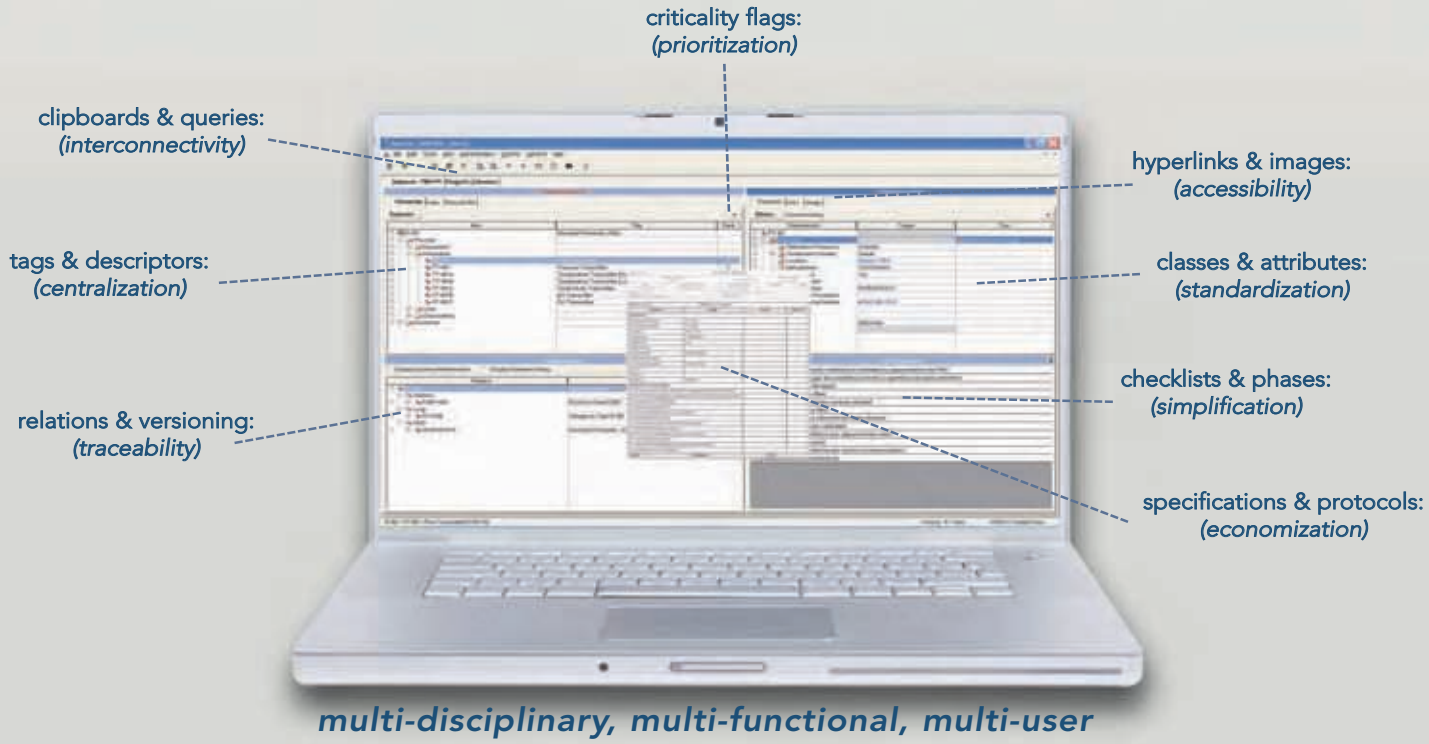


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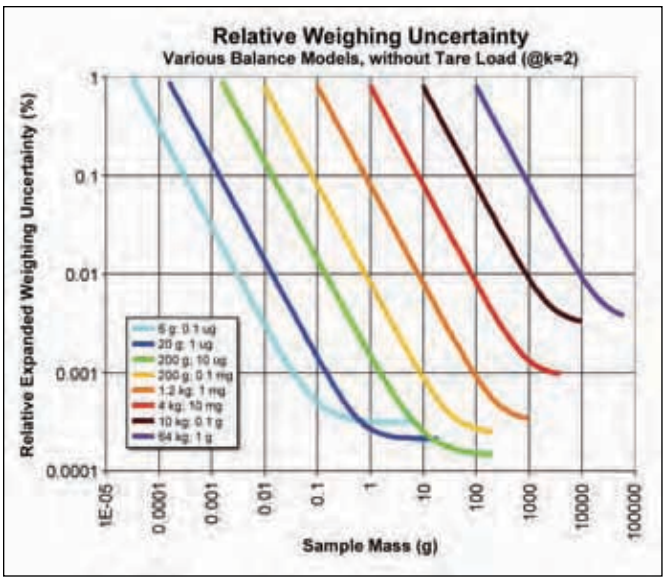


Figure 2. Relative weighing uncertainties of various balances, from an ultra-microbalance with a readability of 0.1ug to a precision balance with 1g. Shown is the relative uncertainty U (in %) versus sample mass m (in g). Uncertainties are estimated from typical specifications of the balances, and are expanded with a factor k = 2, with the assumption of zero tare load (i.e., gross load = sample mass).

There are several properties, quantified in the specifications of the weighing instrument, which limit its performance. The most important are repeatability (RP), eccentricity (EC), nonlinearity (NL), and sensitivity (SE), which are graphically displayed in Figure 1, and in detail explained in the respective technical literature.[4] How do they influence the performance, and hence, the selection of a weighing instrument?

To answer this question, the term "weighing uncertainty" must first be discussed. The "International Vocabulary of Metrology"[5] defines uncertainty as a parameter which expresses the dispersion of the values of a measurement.

The weighing uncertainty, i.e., the uncertainty when an object is weighed, can be estimated from the specifications of a balance (typically, the case when performing a design qualification) or from test measurements with the weighing instrument (typically the case when carrying out an operational qualification or performance qualification) or from a combination of both. The essential influences can be combined according to statistical methods to obtain the weighing uncertainty.[6]

Uncertainty can be expressed either as standard uncertainty $u$ (corresponding to the standard deviation of a statistical process) or as expanded uncertainty $U$, also referred to as "uncertainty interval." To obtain the expanded uncertainty, the standard uncertainty must be multiplied with the expansion factor $k$. Figure 2 shows uncertainties of various balances, which were estimated according to these rules from their typical specifications.

What can be deduced from Figure 2 is that the uncertainties as a function of the sample mass behave similarly for all balance models. It is their "position," i.e., their location relative to the axes of sample mass and uncertainty, which is dependent on the model of balance. The characteristics of this behavior become more obvious from Figure 3, where the individual contributing components are shown. The uncertainty as a function of the sample mass can be separated into three distinctive regions:

1. Region 1 with sample masses less than the lower rollover limit mass (i.e., largest sample mass, at which the contribution of repeatability dominates uncertainty). It is about 10 g in this specific example, and indicated yellowish in Figure 3. As repeatability is a weak function of gross load (if at all), the relative uncertainty decreases inversely proportional to the sample mass.
2. Region 2 with sample masses larger than the upper rollover limit mass (i.e., smallest sample mass, at which the contributions of sensitivity offset and eccentricity dominate uncertainty. It is about 100 g in this specific example, and indicated as greenish in Figure 3). The relative uncertainties of these properties are independent of sample load; consequently, the combined relative uncertainty remains (essentially) constant.
3. Region 3 is the transition region with sample masses between the lower and upper rollover limit mass, where the uncertainty rolls off from inverse proportionality to a constant value.

Moreover, for a majority of laboratory balances, nonlinearity hardly contributes a significant part to uncertainty, as its relative uncertainty, over the entire range of sample mass, is smaller than any other contribution.

### *Essentials to Select a Weighing Instrument*

With these facts in mind combined with the knowledge of the weighing accuracy required for an application and the mass

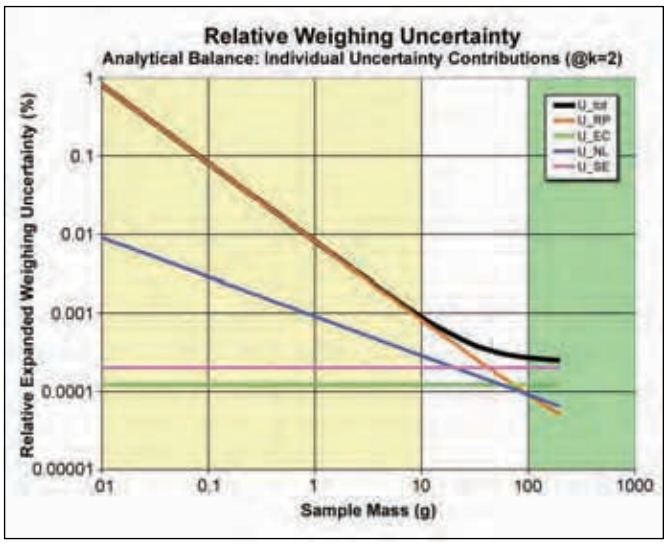


Figure 3. Relative weighing uncertainty versus sample mass (with zero tare load) of an analytical balance with a capacity of 200g and a readability of 0.1g (U_tot, thick black curve). The contributing components to uncertainty also are shown: repeatability (U_RP, orange), eccentricity (U_EC, green), nonlinearity (U_NL, blue) and sensitivity offset (U_SE, pink). Uncertainties are expanded with a factor of k = 2. Repeatability dominates uncertainty in the yellowish region, sensitivity or eccentricity in the greenish region.

*Continued on page 50.*

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of the sample to be weighed, two essential selection criteria for a weighing instrument can be formulated:

1. The capacity of the weighing instrument must be larger than or equal to the largest gross load, i.e., the sum of the tare load and the sample (or net) load to be handled in the application.
2. The uncertainty when weighing the smallest sample must be smaller than or equal to the accuracy required ($A_{req}$) by the user's application.

If a weighing instrument meets these two conditions, it is in principle suitable for the application. The second condition is also known as "minimum weight condition." For a small sample mass, repeatability is the dominating contribution (yellowish region, Figure 3) from which the smallest mass, satisfying the required accuracy, can be calculated. This amount of mass is referred to as "minimum sample weight," or simply "minimum weight." If the minimum weight of a balance is unknown, it can be determined from repeatability. Because a small sample weight lies in region 1, repeatability ($s_{RP}$) is the only balance property on which the minimum weight depends.

$$m_{min} = (k/A_{req}) \cdot s_{RP}$$

As discussed above, it is not the readability that determines the accuracy of a weighing instrument, but rather its repeatability, or depending on it, its minimum weight capability. Note that the determination of the minimum weight from repeatability also is a consequence of the requirement of USP General Chapter <41> "Weights and Balances," which states: "Unless otherwise specified, when substances are to be "accurately weighed" for *Assay*, the weighing is to be performed with a weighing device whose measurement uncertainty (random plus systematic error) does not exceed 0.1% of the reading. Measurement uncertainty is satisfactory if three times the standard deviation of not less than 10 replicate weighings divided by the amount weighed, does not exceed 0.001."[1]

### *Example*

A company needs a balance for their QC department. At a specific point in the weighing process, the mass of samples as small as 20 mg must be determined with a relative weighing accuracy of 0.1%. The gross load is limited to 50 g. What balance suits this application?

From these givens, it can be concluded that any balance with a capacity of 50 g or more (rule 1), and a minimum weight capability of 20 mg or smaller (rule 2) is a candidate for this application. Most likely a semi micro balance (with a readability of 10 ug) would be chosen. If the minimum weight of the balance would not be known, the equivalent repeatability can be calculated instead. With an expansion factor of k=3, and the required accuracy of 0.1%, the equivalent required repeatability is:

$$s_{RP} = (A_{req}/k) \cdot m_{min} = (0.1\%/3) \cdot 20\ mg = 0.007\ mg$$

In other words, a balance with a repeatability of smaller than 0.007 mg has to be chosen to fulfill the user's weighing accuracy requirements.

### *Safety Factor*

Repeatabilities determined from a limited number of on site weighings will vary, even if the setup is left unaltered. Note that the standard deviation of a random variable is itself a random variable. For example, the standard deviation calculated from the readings of 10 weighings of the same object may accidentally exceed the true value of repeatability by as much as 180% or underestimate the true value by as low as 70% on a 95% confidence level.

Besides these statistical variations, environmental conditions, labware used, or the operator may change, influencing the performance of the weighing instrument. Therefore, it is recommended to apply a safety factor (not to be confounded with the expansion factor $k$), which establishes a safety margin between the accuracy limit of the instrument and the required weighing accuracy. It might be advisable to use a safety factor of 2 to compensate for the variation in the determination of repeatability. Note that only the calibration, i.e., the determination of the measurement uncertainty and the minimum weight of the balance at the final installation location, certifies the applicability of the balance for the specific weighing process. The calibration is done by an authorized service technician as part of an integrated qualification approach for the weighing instrument, and is periodically repeated thereafter.

Revisiting our example and applying a safety factor of 2, both the required minimum weight and the repeatability decrease by this factor. The required repeatability thus amounts to 3.5 ug, a value that a semi micro balance may not be able to provide. As an alternative, a micro balance (with a readability of 1 ug) could be used instead.

## Routine Testing of Weighing Instruments

*"Measuring equipment shall be calibrated or verified at specified intervals… against measurement standards traceable to international or national measurement standards."* ISO9001:2000, 7.6 Control of Monitoring and Measuring Devices

*"Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. It is the responsibility of the test facility management to ensure that instruments are adequate and functioning according to their intended use."* OECD Principles of GLP, 4.2 Use, Calibration, and Maintenance of Equipment

The statements cited above delegate the responsibility for the correct operation of equipment to the user. This also applies for weighing instruments. Statements like these are usually formulated vaguely, as they are meant as general guidelines. Therefore, they cannot be put to work for daily routine. Questions like, "How often should I test my balance?" emerge in situations where guidance is needed to design standard operating procedures that neither are too exhaustive, and thus

*Continued on page 52.*

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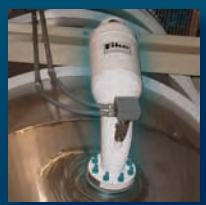

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are costly and time consuming, nor are too loose to assure the proper functioning of a weighing instrument. In order to realize an effective performance qualification as part of a life cycle management approach, the balance properties will have to be looked at a bit closer.

### Routine Test Procedures

Most likely, the majority of all samples being weighed on laboratory weighing instruments, especially in laboratory applications, satisfy the condition of being "small samples," i.e., samples with a net mass considerably smaller than the capacity of the weighing instrument, a few percent of capacity, say. When discussing the relative uncertainty versus sample mass, it was already mentioned that weighing uncertainty is governed by repeatability if a small sample is weighed - *Figure 3*.

Consequently, with the majority of weighing processes, repeatability is the most important contribution to uncertainty. This would be a good reason to test repeatability most frequently. However, this test comprises repeated weighings of the same test weight multiple times, usually around 10 times. To perform these tests properly, considerable effort and elaborated skills are required. On the other hand, the test of sensitivity can be carried out with one single weighing of a test weight, certainly less of an effort. What is more, the sensitivity test would reveal any serious problem with the instrument or if the result were to drift; in short, it may be regarded as an elementary test of the functionality of the weighing instrument. Although sensitivity is not the most critical property of a weighing instrument by far, the sensitivity test is proposed to be carried out with the highest frequency for the reasons cited, followed by repeatability with a lower frequency.

Revisiting Figure 3 and its explanations, it was said that eccentricity influences only weighings of samples with a considerable mass compared to the capacity of the weighing instrument, larger than a few percent, say. Besides, placing containers and samples in the center of the weighing platform or at least in the same place for the tare and the gross readings, the influence of eccentricity can be avoided entirely. This is the reason why eccentricity could be tested less frequently than repeatability or sensitivity. For less demanding applications it can even be dropped, as eccentricity also is assessed when the weighing instrument is calibrated by authorized personnel. For the least demanding applications, even the test of repeatability can be dropped.

Nonlinearity is not recommended to being tested by the user at all, as its influence on weighing uncertainty is inferior and hardly dominant with any model of laboratory weighing instruments; besides, it is being taken care of when the weighing instrument is calibrated by authorized personnel.

The following test procedures for weighing instruments are recommended in the framework of the performance qualification:

1. Calibration by authorized personnel, including the determination of weighing uncertainty or minimum weight, if applicable; the aim is to assess the complete performance of the instrument by testing all relevant weighing parameters of the instrument. Calibration also is an important step within operational qualification after the balance is installed and the necessary functional tests performed.
2. Routine test of sensitivity, repeatability, and eccentricity (but not nonlinearity), to be carried out by the user within defined intervals; the aim is to confirm its suitability for the application.
3. Automatic tests or adjustments, such as those of the sensitivity, carried out automatically by the weighing instrument; the aim is to reduce the effort of manual testing.

### Test Frequencies

The testing procedures and corresponding frequencies are based on:

1. the required weighing accuracy of the application
2. the impact (e.g., for business, consumer, or environment), in case that the weighing instrument should not function properly
3. the detectability of a malfunction

It is assumed that the more stringent the accuracy requirements of a weighing are, the higher the probability becomes that the weighing result does not meet the accuracy requirements. In this case, the test frequency is increased. Similarly, if the severity of the impact increases, the tests should be performed more frequently. That way, a higher impact is offset by more frequent tests, thereby lowering the likelihood of occurrence of the impact, and hence, offsetting the increase of risk that otherwise would occur - *Figure 4*.

If the malfunction of the weighing instrument is easily detectable, the test frequency is decreased.

The frequencies for the test of all properties extend from daily for risky applications (user or automatic tests), over weekly, monthly, quarterly, twice a year to yearly (e.g., calibration by authorized personnel).

### Test Limits – Control and Warning Limit

Routine tests are based on the required weighing accuracy for

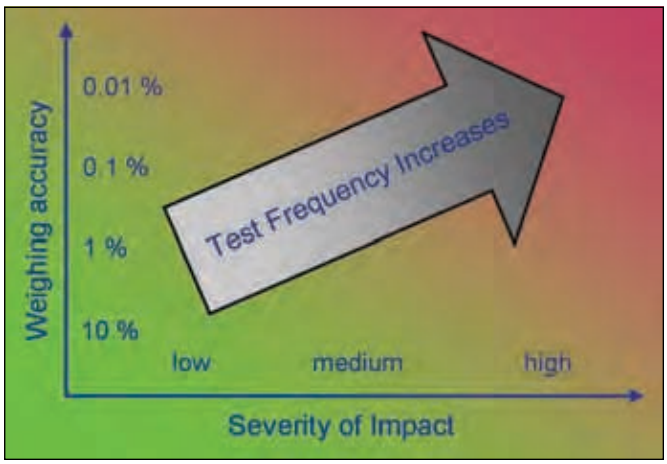


Figure 4. Test frequencies increase as a function of more stringent weighing accuracy and increasing severity of impact in case of an incorrect weighing (qualitative chart).

*Continued on page 54.*


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for an application. Simply speaking, the weighing accuracy must be better than or equal to the accuracy required. The required accuracy is referred to as Control Limit (*CL*), meaning that if this limit is exceeded, immediate action must be taken. It is recommended to introduce a Warning Limit (*WL*), the value of which is smaller than the control limit by a suitable factor, namely the Safety Factor (*SF*) introduced previously. The warning limit is obtained by dividing the control limit by the safety factor $WL = CL / SF$. This allows testing for the warning limit. If the warning limit is violated, there is still a safety margin before a process must be halted. This gives "room" for corrective actions.

Therefore, test results of each individual property are to be compared to warning limits, which in turn depend on the control limits via the safety factor. However, these deviations (sensitivity, repeatability, eccentricity, and nonlinearity) may occur simultaneously; thus, the sum of their deviations may be larger than the warning limit. A simple way to deal with this is to allocate only a part of the warning limit allowance to each individual property. This is achieved by dividing the warning limit by the Uncertainty Combination (*UC*) factor to obtain the test limit against which the individual test results are compared, accounting for the accumulation. For sample masses of a few percent of the capacity of the balance or higher, where repeatability is not dominant, the warning limit allowance is divided by the uncertainty combination factor of $\sqrt{(1+1+1)} \approx 1.73$, taking into account sensitivity offset, nonlinearity, and eccentricity, rounded up (for the sake of simplicity) to 2, yielding the warning limit applicable to each individual property. The warning limits for all properties (with the exception of repeatability) are obtained as follows:

$WL = m_T \cdot A_{req}/(SF \cdot UC) = ½(m_T \cdot A_{req}/SF)$ (limit value for sensitivity offset, nonlinearity, and eccentricity)

where $A_{req}$ is the required relative accuracy, *SF* the safety factor, $m_T$ the mass of the test weight.

Repeatability dominates uncertainty in region 1 (Figure 3, yellowish). In a laboratory environment, by far the most number of weighings of sample masses will occur in this region. Because in this region, the contributions of sensitivity offset, eccentricity, and nonlinearity to the overall weighing uncertainty are negligible compared the repeatability contribution, the allowance of repeatability needs not be reduced; thus, can be directly compared to the warning limit. Moreover, the standard deviation of repeatability is already expanded by $k$, the coverage or expansion factor.

For repeatability, the warning limit is expressed as standard deviation:

$WL = m_{S,min} \cdot A_{req}/(SF \cdot k)$ (limit standard deviation for repeatability)

where $m_{S,min}$ the mass of the smallest sample to be weighed and $k$ the expansion factor.

Figure 5. Two test weights are recommended. The large weight has a mass close to the nominal capacity of the weighing instrument, while the small weight amounts to a few percent of the nominal capacity. The large weight is used to test sensitivity and eccentricity, the small for repeatability (if required, together with an additional tare mass).

### Test Weights

"Which weight should I use to test my balance?"

For the user tests, two test weights are recommended - *Figure 5*.

1. A large weight preferably of a mass equal to the capacity of the weighing instrument. It is recommended to use the next available single weight denomination according to the OIML or ASTM classification, which is smaller than or equal to the nominal capacity of the weighing instrument.

2. A small weight preferably of a mass equal to a few percent of the capacity of the weighing instrument. It is recommended to use the next available single weight denomination according to the OIML or ASTM classification, which is smaller than or equal to 5% of the nominal capacity of the weighing instrument.

As further guidelines, the following rules are implemented:

1. Weights for the test of the sensitivity of weighing instruments need to be calibrated and must be traceable (reference weights). Their maximum permissible error (mpe) must not be larger than 1/3 of the warning limit so that its influence compared to the warning limit may be neglected. With this condition, the contribution of variance of the test weight is limited to less than 10% of the variance of the warning limit. The lowest weight class which fulfills this condition is selected. Since the warning limit depends on the control limit, and thus on the required weighing accuracy, so does the mpe of the test weight.

2. All other tests (i.e., tests of repeatability or eccentricity) may be performed with any weight, provided it does not change its mass during the test. Of course, it is always possible to use a calibrated test weight for these tests as well, but this is not required.

3. According to Figure 3, testing for sensitivity with a test weight which is too small (compared to the capacity

of the weighing instrument) runs the risk of the test measurement becoming "contaminated" by the influence of repeatability.

Test weights for sensitivity are typically of higher accuracy class (OIML F or E). However, even in cases where an OIML class M weight would suffice for a test, OIML class F2 weights should be used instead. The reason is that the surface of class M weights is allowed to remain rough.[7] This increases the chances for potential contamination, a feature which is not tolerated in laboratories. The same applies for ASTM weights where weight classes lower than ASTM4 should not be used in a laboratory environment.[8]

Test weights for sensitivity must be (re-)calibrated themselves in regular intervals to provide traceability.

### User Routine Tests

The following tests are recommended:

1. Sensitivity preferably with the large weight. At the user's discretion, the test can be performed with the small weight or at an arbitrary "operating point." However, there is a potential loss of test selectivity when using a small weight, i.e., the sensitivity test becomes contaminated by repeatability deviations - *Figure 3, region 1*. This may especially apply to test weights smaller than the second weight recommended.

2. Repeatability preferably with the small weight. It is recommendable to involve in the repeatability measurement tare weights or containers that will be used later. Tare weights, or even more so, vessels may degrade repeatability.[9]

3. Eccentricity preferably with the large weight.

Reassessing the example of weighing 20 mg with an accuracy of 0.1% (expansion factor $k$=3) on a micro balance with a capacity of 50 g, thereby applying a safety factor of 2, we are now able to determine the control and warning limits for the tests to be carried out with the two weights that are considered - *Table A*.

### How to Assess Repeatability?

As pointed out above, the majority of weighing processes take place with small samples. This is the case in a laboratory when weighing small amounts of substance in a vessel, for example. Therefore, it is reasonable to test the repeatability with a test weight in the order of a few percent of the capacity of the weighing instrument, rounded to the next weight denomination. While repeatability generally tends to increase with increasing gross load, this increase is usually feeble, a factor of 2 from zero load to nominal capacity, for example. Nevertheless, repeatability may be regarded as essentially constant for small sample weights, i.e., weighing processes

*Continued on page 56.*

| Balance capacity 50 g | | | Sensitivity | | Repeatability | | Eccentricity | |
|---|---|---|---|---|---|---|---|---|
| Smallest net weight 20 mg | | | CL | WL | CL | WL | CL | WL |
| Required accuracy 0.1% | | | | | | | | |
| Expansion factor k = 3 | | | | | | | | |
| Safety factor SF = 2 | | | $½(m_T \cdot A_{req})$ | $½(m_T \cdot A_{req}/SF)$ | $m_{S,min} \cdot A_{req}/k$ | $m_{S,min} \cdot A_{req}/(SF \cdot k)$ | $½(m_T \cdot A_{req})$ | $½(m_T \cdot A_{req}/SF)$ |
| Weight 1 | ≤ 100% of capacity | 50 g | 25 mg | 12.5 mg | --- | --- | 25 mg | 12.5 mg |
| Weight 2 | ≤ 5% of capacity | 2 g | --- | --- | 6.7 ug | 3.3 ug | --- | --- |

Table A. Example for calculating control and warning limits for user routine tests (sensitivity, repeatability, and eccentricity).

where the tare and gross loads are close to each other and therefore both readings exhibit essentially the same repeatability. This fact is depicted in Figure 6. It can be seen that the (absolute) uncertainty, and therefore the repeatability, as all other contributions are negligible, remains essentially constant for small sample weights (compared to the capacity of the balances).

If repeatability is a critical issue, it is recommendable to put the tare object (container, vessel, flask, etc.) on the weighing platform and to test repeatability with the test weight at this "working point." It should be mentioned here that not only the mass of a tare load, but also its dimensions may influence the repeatability of the weighing. On a semi micro balance, for example, repeatability might increase about five times when weighing a sample into a volumetric flask of 250 ml, compared to weighing the sample together with a compact tare of the same mass as the flask (around 90 g).[9]

### *Why can the Minimum Weight be Determined with a Test Weight Larger than the Minimum Weight?*

By definition, minimum weight is the lowest amount of sample mass that can be weighed, complying with a given required weighing accuracy. The most obvious method to test for minimum weight is to use a test weight with a mass of the (expected) minimum weight and determine the repeatability of the weighing instrument with this test weight. If the resulting weighing uncertainty is smaller than the required accuracy, the test passes, if it is greater, the test fails.

This method has several disadvantages:

First, if the test passes, there is no guarantee that there might not be still a smaller mass satisfying the accuracy requirements. To find out about this, the test needs to be repeated with a smaller test weight.

Second, if the test fails, the test needs to be repeated, too, but this time with a larger test weight. In both cases, the test may require an iterative approach, demanding more effort than just for one test. This is a waste of resources.

Third, using OIML test weights, as is very convenient, come only in denominations of 1-2-5 (for ASTM weights, the dominations are 1-2-3-5, accordingly). This means that a minimum weight of 45 mg, for example, could not be confirmed, unless the test is carried out with a weight combination of three weight pieces, namely 20 mg, 20 mg, and 5 mg. Needless to say that determining the repeatability with a test load composed of three test weights is a tedious and error prone task.

Fourth, minimum weight of analytical and microbalances are in the order of a few milligrams. Handling such a small weight is difficult, and the faintest draft may blow the weight away.

There is a more efficient method to test minimum weight. It bases on the fact that with all balances, repeatability is no function of sample mass, i.e., remains constant, as long as the sample mass is smaller than a few percent of the weighing capacity. With this knowledge, it becomes clear that the repeatability need not be determined with a test weight of the very minimum mass, but can be chosen larger, as long as the condition stated is met. The repeatability obtained from this test can then be used to calculate the minimum weight.

$$m_{min} = (k/A_{req}) \cdot s_{RP}$$

The advantages of this method are manifold:

- Only one test must be performed.
- The mass of the test weight can be chosen so that the test can be conveniently carried out.
- Intermediate, i.e., non 1-2-5 (1-2-3-5) values for the minimum weight are possible.

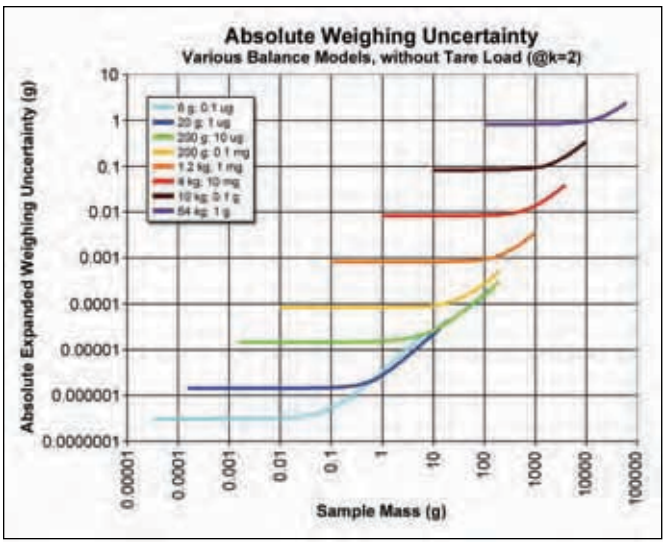


Figure 6. Weighing uncertainties of various balances, from an ultra-microbalance with a readability of 0.1ug to a precision balance with 1g. Shown is the (absolute) uncertainty U (in g) versus sample mass m (in g). Uncertainties are estimated from typical specifications of the balances, and are expanded with a factor k = 2, with the assumption of zero tare load (i.e., gross load = sample mass).

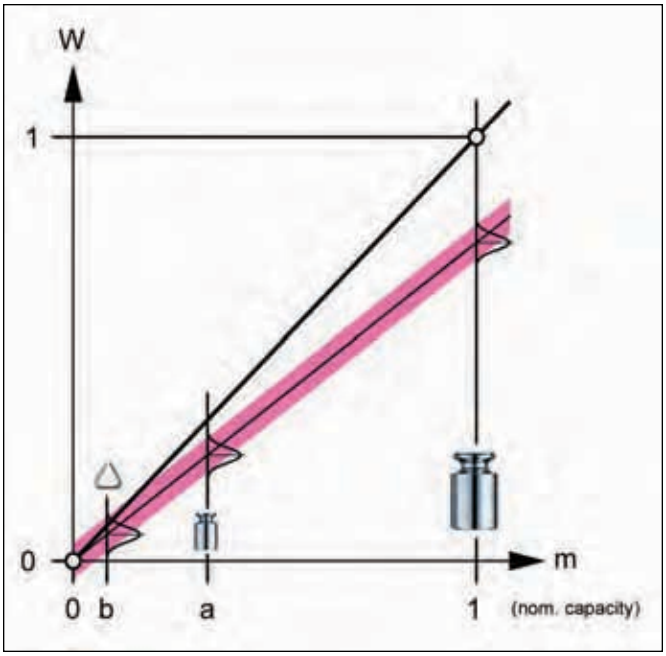


Figure 7. Sensitivity of a weighing instrument: shown is the displayed weighing value W versus the load m on the platform. To test for sensitivity, it is recommended to use a test weight close to nominal capacity.1 Using a smaller test weight (a < 1) results in a smaller measurable sensitivity offset, which is partially disturbed by repeatability (red band). Using a very small test weight (b < < 1) results in a measurable sensitivity offset which is buried entirely in the dispersion band of repeatability. (Remark: This diagram, and particularly the test masses of (a) and (b) weights, are not shown to scale.)

This fact also is considered in the latest draft revision of USP General Chapter <1251> "Weighing on an Analytical Balance" - *Table A "Suggested Performance Qualification Tests."*[10]

### *Why should a Test Weight Close to Capacity be Chosen for the Test of Sensitivity?*

Referring to Figure 3, region 1, where the sample mass is smaller than the lower rollover limit mass, 10 g in this example, it was said that repeatability dominates the uncertainty, i.e., all other properties (sensitivity, eccentricity, and nonlinearity) contribute negligible amounts to uncertainty, compared to repeatability. A test result in this region is contaminated by deviations caused by repeatability, the more so, the smaller the test weight becomes. Simply speaking, sensitivity is buried in repeatability - *Figure 7*. Therefore, a test weight close to capacity should be chosen.

### *Instruments with Automatic Test and Adjustment Features*

"What is the importance of the adjustment with built-in weights versus a test with an external weight?"

Adjustment mechanisms built into weighing instruments consist of one or more reference weights, and a loading mechanism that is actuated either manually or automatically. Such a mechanism makes it possible to conveniently test or adjust the sensitivity of the weighing instrument. Because the built-in weight cannot be lost, cannot be touched, and is kept in a sheltered place inside the instrument, this concept has advantages over testing or adjusting with an external weight, which is vulnerable to damage, dirt, and other adverse effects; besides, it allows to substantially reduce the frequency of such tests or adjustments with external reference weights.

However, because the built-in test weight is not accessible, it cannot be declared as being traceable since traceability requires that the weight can be removed and compared periodically with another reference of a higher class, which is not possible. Nevertheless, the built-in weight can be tested against an external reference by comparing the weighing result of the built-in weight with the weighing result of an external reference weight, which is weighed immediately thereafter, the very weighing instrument being the comparator. With this comparison, the integrity of the built-in calibration mechanism can be tested.

If a weighing instrument features such an adjustment mechanism, it should be (frequently) used, as it is a procedure that requires little to no effort with the exception of a short interruption of use to the instrument. As a consequence, routine tests of sensitivity with external reference weights may then be performed less frequently. This fact also is reflected by an important statement of the US Food and Drug Administration: "For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature."[11]

## Conclusion

By implementing Good Weighing Practices as a methodology to provide a risk-based life cycle approach for evaluation, selection, and routine testing of balances, measurement errors can be reduced and reliable weighing processes can be realized.

For a specific weighing process, two key issues are to be considered for a successful selection of weighing instruments:

- The weighing capacity must be larger than the largest gross load expected to be weighed by the user.
- The minimum weight of the weighing instrument for the accuracy required must be smaller than the smallest sample expected to be weighed by the user.

To achieve periodic verification of laboratory weighing instruments within an integrated qualification approach, the following procedures should be carried out:

- calibration by authorized personnel (a service technician, for example)
- routine tests to be carried out by the user
- automatic tests or adjustments affected by the instrument

The testing procedures and corresponding frequencies are based on:

- the required weighing accuracy of the application

*Concludes on page 58.*

- the severity of impact (e.g., on business, consumer and environment), in case that the weighing instrument should not deliver the correct weighing result (malfunction)
- the detectability of such a malfunction

The recommended test frequencies are increased with higher accuracy (i.e., more stringent requirements) and with increasing severity of impact, and are decreased with detectability of a malfunction. On the other hand, for less stringent process requirements and reduced risk, test efforts can be reduced accordingly. This strategy reflects current thinking about implementing a risk-based approach in qualification and validation activities.[12,13]

An understanding of the weighing process requirements together with an understanding of the basic principles of balance properties as weighing uncertainty and minimum weight enables the user to realize an integrated qualification strategy as a basis for achieving qualified weighing processes. Risk- and life cycle management thereby form an integrated part of an overall strategy to bridge the gap between regulatory compliance, process quality, and cost consciousness.

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**This article discusses why Construction Quality Management (CQM) is the key to delivering successful capital projects and outlines some of the challenges encountered from a construction/ field execution perspective, rather than design/ engineering perspective. It highlights the pivotal role of CQM in ensuring that a facility has good operability and availability as well as high reliability and maintainability.**

# Construction Quality: the Key to Successful Capital Projects Delivery

by Jay Lad and Bruce Beck

## Introduction

What is deemed a successful capital project? Is it one which is built on time, within budget, in a safe manner with good design and great quality?

Many, in short, would answer yes. However, the true success of a project should be judged on how well the facility performs from an operability, availability, reliability, and maintainability perspective. This is the real test on how good a facility has been designed and built! Therefore:

***A successful project is where a facility reaches optimal operation, in a safe manner, and in the shortest possible time-frame, generating cash at the earliest possible opportunity.***

***A successful project is where a facility achieves a high availability and reliability during the first-cycle operation, maximizing cash flow through the first-cycle operation.***

## Background

The life sciences sector, predominantly a regulated industry, is well served from a design/ engineering perspective. It has many design guides readily available, such as the ISPE Baseline® Guides and GAMP®, ASTM E2500, etc. Designing quality into a facility has become the standard and the norm for biopharmaceutical facilities. Also, the culture of Good Engineering Practice (GEP) and Good Documentation Practice (GDP) is a well established concept across many market and industrial sectors.

However, a well designed facility with excellent quality and specification has little or no value if the design is not properly translated into the construction and start-up of the facility.

There are many different delivery methods for capital projects; however, all approaches tend to involve taking a design, breaking it down into manageable packages, and sub-contracting the work packages in a manner which will allow the constructor to reduce his risks and make a reasonable fee on the project. Therefore, a constructor does not really build a facility; he simply selects and manages sub-contractors.

***Therefore, the facility one builds is as good as the selection and management of the sub-contractors!***

In general, biopharmaceutical facility design/ construction is an "evolving/changing" world. It is a world where ideas, concepts, and designs are developed by engineers/scientists and which constructors attempt to bring to reality. Often, at the design phase of a project, the products are still in the development phase and yet to be fully characterized and understood. As a result, aspects of the facility often evolve and change during the design and construction phases of the project. In some extreme cases, the facility can be completely redesigned mid way through a project.

However, in stark contrast, the world of pharmaceutical manufacturing is a "precise" world, heavily scrutinized and under strict Quality Assurance/Quality Control (QA/QC) control. It can be characterized by its "batch sheet" mentality.

For a long time, engineering groups have been trying to apply the batch sheet mindset to the evolving/changing world of engineering and construction, often resulting in escalating costs and large program over-runs/delays.

The biopharmaceutical industry is very competent in the QA/QC of its manufacturing processes, but struggles to extend this competency in quality to the delivery of capital

projects. Delivery of capital projects and construction quality are not always the core competencies of the owners; however, it is extremely important to a successful project.

Construction companies tend to be field execution driven with their focus on safety. Ideally, safety and quality should be combined to deliver projects with zero accidents and zero defects/punch lists. Using industry standards, such as ISO9000, can assure that construction companies have fundamentally sound management practices and a foundation for quality.

At the outset of a project, the appropriate level of quality must be determined for all phases of the project. This is usually established for the engineering and the qualification phases of the project. However, it is usually overlooked for the construction and commissioning phases of the project, probably the two most critical phases of the project that impact operability, availability, reliability, and maintainability of a facility.


Figure 1. Commissioning flowchart.

*Continued on page 62.*

At the start of a project, the start date and end dates are usually set in stone and it is usual for the design, engineering, and construction phases of the project to over-run. However, there is not much room for the commissioning phase of the project to over-run, as it is the penultimate phase of the project, prior to qualification and handover to the client. It also is one of the most critical and hazardous phases of the project, largely due to the fact that systems are energized and started-up.

A good constructor should normally have a commissioning plan developed at the pre-construction stage of a project. The objective being that the most critical and dangerous parts of the project is fully mapped out and costed, even before the construction has started. (See Figure 1 for an approach to commissioning).

However, a well planned commissioning program with excellent protocols and check sheets is of no value if the construction of the overall facility is of a poor quality and littered with defects. Therefore, the overall commissioning effort will ultimately prove to be more hazardous, troublesome, and costly.

It is clear from the above that at the pre-construction stage of the project, the approach to construction quality should be fully established in a construction quality plan. The level of quality to be applied to the project should be clearly laid out and fully understood by all parties.

The term "quality" in the life sciences industry has significant connotation and emphasis as absolutely central to the mission of the business. The concept of quality also has importance in the construction industry, especially in the delivery of new or modified biopharmaceutical facilities. The type of quality issues addressed during the construction phase may range from potential product quality impacting issues to more commonly quality deficiencies that are an operational and/or maintenance type issue (e.g., heat tracing for external piping not installed properly, resulting in frozen pipe work during extreme cold weather conditions). These types of quality issues are often a nuisance and costly to address after construction handover. They also can hinder operability, availability, and reliability of facilities.

Establishing a culture of quality within an organization is not something that can be implemented quickly. It requires a complete turnaround in corporate culture and management approach as compared to the traditional way of top management giving orders and employees merely obeying them. It's also a slow and gradual process, which requires substantial investment and commitment, which may not always make commercial sense in the construction industry. The main two factors which may cause this are highlighted below:

- **Product Diversity**
  All buildings/facilities are unique. Quality is seen as consisting of those features, which meet the specific needs of an industry, market sector, or customer and thereby provide satisfaction, supplemented with a proviso of freedom from defects.
- **Organizational Stability**
  The construction industry has a high number of collapses, especially during a downturn in the economy. Thus, commitment toward quality strategies and policies that may take several years to provide "pay offs" may be perceived as futile or a misdirection of resources. As compared to the head office, the construction site is transitory. Teams specially formed for a project may cease to exist after contractual obligations end. Add to this the fact that the implementation of quality in construction requires the selection of the appropriate sub-contractors who would commit to the quality process and develop a true quality attitude.

From the above, it would appear logical in some instances to have the construction quality function managed by a third party; one who really understands field execution, safety, and can bring the appropriate level of quality to the field game of construction.

Figure 2. Integrated Commissioning and Qualification (ICQ) flowchart.

Is it the architect, engineer, or would it make more sense to have a commissioning firm work closely with the construction company to integrate quality into construction and hence leveraging this into commissioning and qualification. (See Figure 2 for an integrated approach to commissioning and qualification).

A commissioning firm which understands field safety, construction quality, and qualification requirements may be ideally placed to take on the role of "Construction Quality Management (CQM)." If executed properly, not only can this role be carried out in a cost effective and independent manner, but also add great value to both the constructor and the end client.

So how can a commissioning company deliver the right quality to the construction activities in the field? This can be achieved by adapting the principles of Good Engineering Practice and Good Documentation Practice to suit construction.

This section outlines the general process that could be employed in the execution of quality management of construction projects. The program should be tailored for each project to ensure proper levels of continuing quality are achieved. The program should form the basis of, and should be a prerequisite to successful commissioning and qualification.

## Construction Quality Management (CQM) Program

The Construction Quality Management (CQM) program is the enabling process that allows clients to use other construction contractors with varying levels of regulated industry project expertise, yet be assured that the outcome is a trouble-free commissioning, qualification, and validation execution ensuring a reduced time to market.

The overall approach is to apply quality concepts and practices to the construction activities to ensure that the facility is delivered on time, as specified, defect free and in an operable state. One of the primary objectives of the CQM Program is to raise the importance of "quality" and "self inspections" to the constructor/sub-contractors in order to prevent deficiencies, minimize defective work, and strive toward a zero critical items punch list.

Ultimately, a facility with a good construction quality program and minimal defects is more likely to have a smooth and trouble free transition into the commissioning/qualification phase of the project.

The CQM Program should ensure proper construction turnover and that systems are ready for commissioning. For GMP critical systems, enhanced commissioning should then be performed to ensure that commissioning activities and documentation can be leveraged into qualification, hence, reducing time-to-market.

The level of quality for any project is defined by the contract requirements, drawings, specifications, current Good Manufacturing Practices (cGMP) and approved quality assurance/quality

*Continued on page 64.*

control guidelines.

As the design begins to crystallize during the development stage, the CQM Manager in conjunction with the client should begin to develop a project specific Construction Quality Plan, documenting the key steps it will take to deliver a building/facility that is fit for purpose. It is crucial to establish clear goals and objectives for the project, which will establish an appropriate level of quality expectations. As soon as the goals are set, the CQM Manager should develop a detailed Construction Quality Plan encompassing:

- Roles and Responsibilities
- Submittal Quality Management
- Subcontractor Quality Management
- Definition of Required Turn-Over Documentation
- Material and Field Quality Management
- Discrepancy Management and Control
- Training of Client personnel
- Hand-Over to Client

In order to effectively manage and execute the construction quality, the Construction Quality Plan needs to be part of an overall CQM Program. The CQM Program should form the basis for integrating construction with commissioning. The aim of the CQM Program is to reduce cost and time to market through a number of critical steps as identified below - *Figures 3 and 4*.

### *1. Risk Assessment and Criticality Analysis*

At the start of a project, it is important to identify and understand critical aspects of the entire project that will impact schedule and cost.

Currently, risk analysis is carried out at the design phase of a project, by the engineers and end users, usually from a design and engineering perspective. The result normally captures the client's expectations by classifying systems into critical/direct impact systems and non-critical/indirect impact systems. This is obviously significant because critical systems, or higher risk systems, require a higher level of documentation and field inspections.

However, it is just as important to identify and assess the risks to the project from a field execution perspective. Therefore, at the pre-construction stage, the risk assessments also should be carried out from a field perspective, identifying/assessing the criticality and interdependencies of systems, not just from a quality perspective, but also from a schedule impact perspective. This should apply to all systems, not just GMP impacting systems, and should be carried out by the CQM manager, constructor, and the client. A risk assessment, which is executed from both a "quality" and "schedule" perspective, will allow the field team to focus with the end in mind.

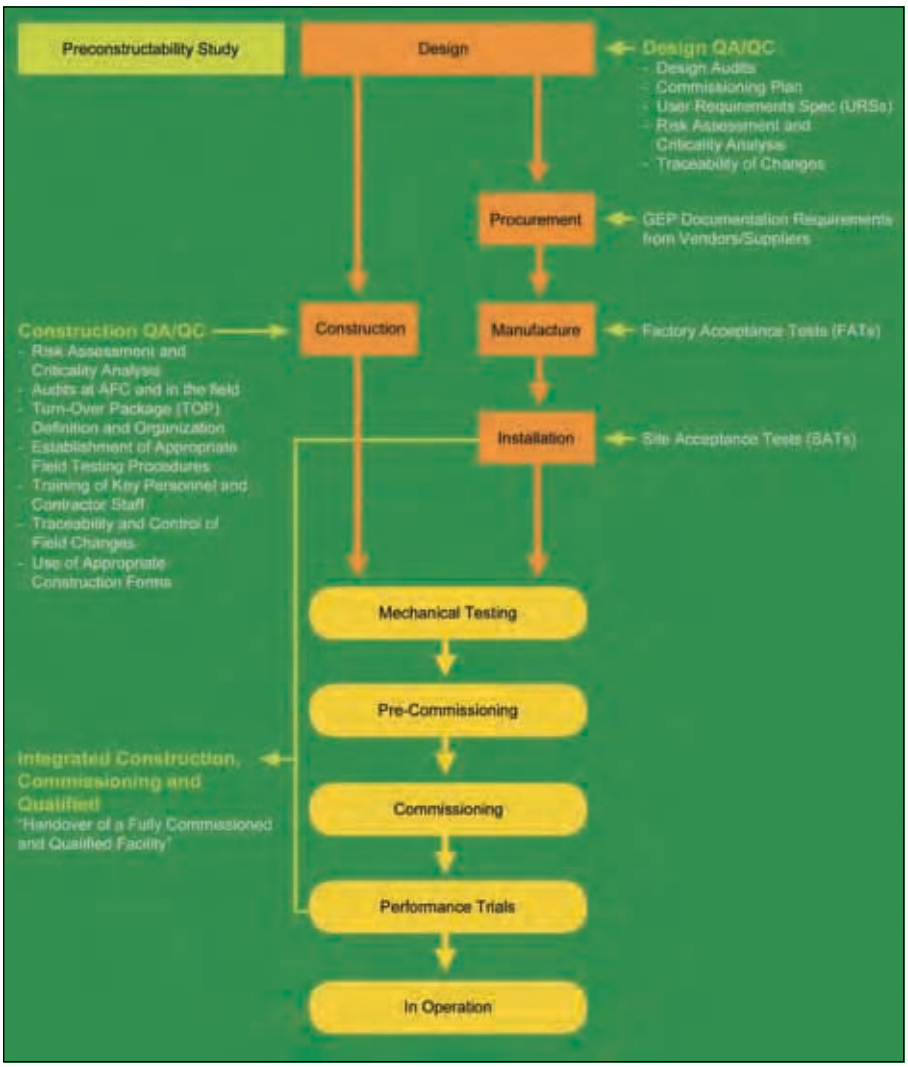


Figure 3. Approach to project quality.

### *2. Audits for Approved for Construction (AFC) Drawings and in the Field*

Compliance audits are normally carried out at the design phase of a project, by the engineers and end users, usually from a GMP/GEP perspective. The result normally captures a lot of potential issues, largely from a regulatory, operability, and maintainability perspective. However, often little or no auditing is carried out from a construction/field execution perspective.

The CQM manager should perform field audits, focused on high risk/critical systems that have been identified during the risk and criticality analysis. The primary objective of the field audits should be to highlight construction quality issues that may impact start-up/commissioning, and hence, the overall project schedule. The field auditing should be supported by a formal process

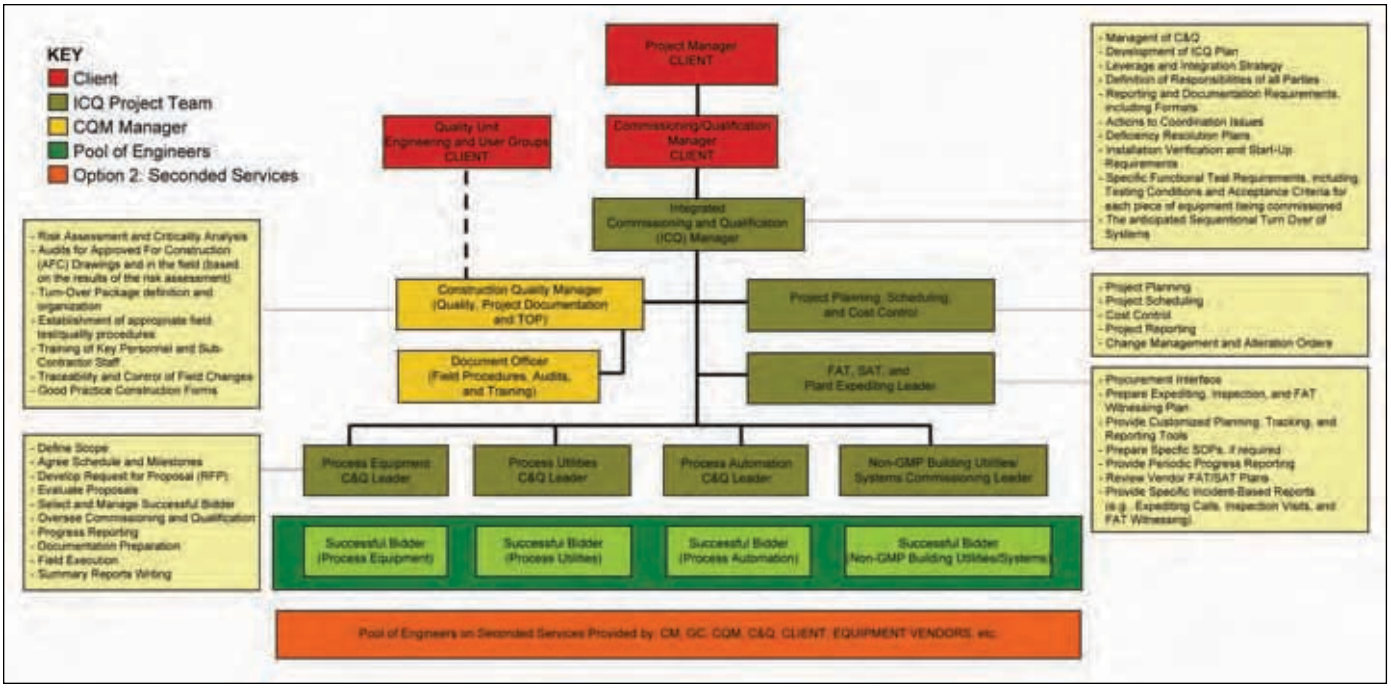


Figure 4. Project execution organization.

to record, manage, and resolve issues.

Ideally, the CQM manager also should perform compliance audits on "Approved for Construction" documentation prior to start of work as well as review bid packages to assure that the requirements of the operating company are included and delivered. This is applicable to both vendors and sub-contractors. Regular

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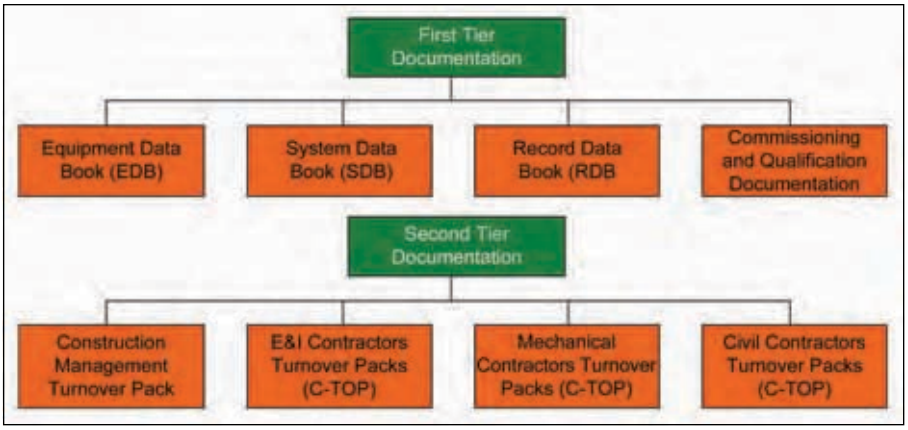


Figure 5. Turn-Over Package (TOP) organization.

meetings should be held with vendors/sub-contractors in order to ensure that specifications are understood and appropriate procedures are in place.

### 3. Turn-Over Package (TOP) Definition and Organization

The CQM manager should develop the Turn-Over Package (TOP) procedure, ideally at the preconstruction stage of the project. This procedure should be discussed and agreed with the constructor and sub-contractors as they will ultimately be responsible for assembling the TOPs. The CQM manager should audit the development of the TOPs and conduct a final review at hand-over stage. This should guarantee a high quality package, which should include all required up to date documentation from vendors, engineering, CM field activities, procurements, etc.

The organization of the TOP is extremely critical to the success of the qualification process; therefore, it must be structured and indexed in such a way that the client is able to leverage the documentation and data into qualification.

However, the TOP also is critical from an operation and maintenance perspective. Once the facility has been completed, the commissioning and qualification documentation will certainly support the regulatory effort. However, a good TOP also should consider how the facility will be operated and maintained after hand-over and what documentation will be required to achieve this. Figure 5, illustrates a two tier TOP architecture. The first tier documents are those deemed to be critical to plant operation, commissioning and qualification. The second tier documents are largely those documents that will be referenced by the first tier documents.

- Tier 1: Equipment Data Book (EDB)
  The EDB should provide plant engineers, supervisors, and maintenance personnel with an accurate reference file for maintaining the plant equipment to the optimum performance level. These files should contain all information relevant to a piece of equipment grouped by area and purchase order. The bulk of this information should be made up from vendor supplied documentation.

- Tier 1: System Data Book (SDB)
  The SDB should provide information to a particular part of the plant set by system boundaries. The SDB should aid plant engineers, supervisors, and maintenance personnel with an accurate reference to the location of equipment, instruments, system boundaries, etc. for maintaining the plant equipment to the optimum performance level. Where documentation is not inserted in the SDB, but required for the system, reference should be made to the documents location, i.e., equipment data files, contractor turn over packs, etc.

- Tier 1: Record Data Book (RDB)
  The RDB should contain all records, latest revisions of drawings, and detail documentation for the project. Ideally, this should be broken out by discipline. In general, the RDB also should provide useful information for plant engineers, supervisors, maintenance personnel, as well as regulatory authorities.

- Tier 1: Commissioning and Qualification Documentation
  The commissioning and qualification documentation should be a collection of documentation packs generated by commissioning and qualification engineers to prove systems, plant, and equipment are acceptable for production and where applicable to regulative authorities.

- Tier 2: Construction Management Turnover Pack
  Construction Management TOP should be a collection of construction documentation generated by construction manager's sub-contractors and should include:
  - Electrical and Instrumentation Contractor's Turnover Packs
  - Mechanical Contractor's Turnover Packs
  - Civil Contractor's Turnover Packs

### 4. Establishment of Appropriate Field Procedures

The CQM manager should identify and establish appropriate field testing procedures necessary to execute the project. The field testing procedures may include procedures that govern protocol and documentation formats, testing and inspection procedures (as occasionally provided by sub-contractors as part of their quality program), documentation storage and distribution procedures, and project punch-list procedures.

### 5. Training of Key Personnel and Contractor Staff

The quality culture of "right first time" should be developed within the project team through a training program. All key construction personnel and sub-contractor staff directly involved in completing documentation for project turn-over packs should be trained, as a minimum, in Good Documentation Practices, as well as relevant SOPs

and field procedures established for the project.

### *6. Traceability and Control of Field Changes*

During the design/engineering phase, design changes are usually managed and controlled extremely well. However, the management and control of field changes is usually overlooked. Often there are more changes in the field then there are in the design phase. Therefore, traceability and control of field changes should be a high priority for the overall project team, as field changes may compromise operability, safety, quality, schedule, and costs.

The CQM manager should ensure, as a minimum, that field changes are properly assessed from a safety, quality, schedule, and costs perspective. He also should ensure that the field changes are recorded, properly documented, dated, assigned accountability, audited, signed, and properly filed. "Red flag" items should be prioritized for action.

### *7. Use of Appropriate Construction Forms*

All check forms to be used for system fabrication, installation, and testing should be in compliance with Good Engineering Practice requirements. The forms also should be checked for suitability and contents as they may be used as leveraged data, hence, eliminating duplication of effort.

## Case Study: Construction Quality Management (CQM)

### *Background*

In 2002, Eli Lilly committed to build a new biotech facility in the USA, which was critical to its long term strategy in biotechnology. The facility incorporated nearly 500,000 sq. ft. of laboratory, pilot plant, and administrative space and cost more than $200 million.

Several years prior to this project, Lilly had spent significant effort in strengthening its Commissioning and Qualification (C&Q) programs throughout the corporation. These improvements were based largely on the ISPE Baseline® Guide for Commissioning and Qualification, Volume 5. This effort had resulted in the development of a well defined and structured C&Q program, which helped deliver a better quality of deliverables, but most importantly, provided significant cost and schedule savings in the delivery of capital projects. As a result of this effort, Lilly's Corporate C&Q Group recognized that "construction quality" was critical to the success and efficiency of the overall C&Q effort. As a result, Lilly set up focus groups which begun working with contractors in order to identify critical factors that improved construction quality. These focus groups in conjunction with local contractors, identified critical steps that affected construction quality and began implementing them on various projects that were being executed by Lilly.

When Lilly issued the request for proposal for the new biotechnology facility, it included a requirement

*Continued on page 68.*

that bidders submit their Corporate Construction Quality Program and specifically their plan for managing quality on Lilly's new biotech project. The ability to clearly articulate a well defined construction quality program/approach for the project was a significant factor in awarding the contract.

### *Construction Quality Management (CQM)*

Following award of the contract, Lilly chose to appoint a third party CQM manager to help manage the overall construction quality for the project. The CQM manager worked in partnership with Lilly to set-up a CQM program to provide "quality" oversight, similar to programs used for contractor "safety" and worked closely with the Lilly C&Q team. At the outset of the project, both Lilly and the CQM manager recognized that this was a learning opportunity for understanding how to effectively manage construction quality and understand the benefits.

The CQM manager performed inspections, but did not take responsibility for quality away from the contractors. The CQM manager's activities included, but were not limited to the following:

- auditing the contractor's quality program to assure it was functioning
- holding meetings with sub-contractors to review job quality plans (required for sub-contractors)
- holding weekly quality meetings to review and follow-up on quality issues discovered on the project
- performed job site inspections across multiple phases of the project and tracked and reported metrics to Lilly and the contractor

As the project progressed, it became apparent that meeting the project completion date had become paramount for the business owner to meet critical business objectives.

### *Findings*

The CQM effort identified and managed a considerable number of construction related quality issues throughout the construction phase of the project. The types of findings varied significantly in potential impact on cost and schedule.

Some findings were relatively minor in potential impact on cost/schedule, while others had the potential to significantly delay the commissioning/qualification phase of the project. In one particular case, a quality issue had the potential to cause major catastrophe had it not been identified and resolved early in the project by the CQM team.

Findings were recorded in Quality Observation Reports (QORs) and entered in a database with a unique identifying number. (There are various off-the-shelf databases commercially available such as Latista, Vela Systems, etc.).

In many cases, a photograph also was taken and captured in the data base, together with the QOR. The photographic records proved to be extremely useful because these enabled field issues to be visually displayed to the sub-contractors, which in turn helped clarify the issue and avoid further discussions/debates. In addition, a date for resolution of each issue was assigned to each QOR. Weekly quality meetings also were held by the CQM group together with the sub-contractors, in order to discuss new findings and status of previous findings. These meetings were extremely valuable in maintaining focus on field issues and driving resolution. The proactive and systematic management of the field issues prevented the typical build up of issues at the end of the project.

Typical examples of field issues that were identified included:

- Steel Shear Tears
  Shear tears were noticed on the ends of multiple support angles being used in building erection - *Figure 6*. It was confirmed that the tears were preventing the welds from penetrating the steel. The welds were not bonding the steel in any way. As a result, all steel angles were repaired to provide efficient bonding surfaces before installation. Analysis was completed to prevent future occurrences. This was primarily a structural issue, which if undetected and unresolved

| | | Potential Impact | | | | |
|---|---|---|---|---|---|---|
| **Example Issues** | **Type** | **Catastrophic Failure** | **C&Q Delay** | **General Delay and Repair** | **Safety** | **No Impact** |
| Roof Drains Installation | Mechanical | | | X | | |
| Weld Quality | Mechanical | | X | X | | |
| Welding Log Documentation | Mechanical | | X | | | |
| Missing Instruments | Mechanical | | X | | | |
| Equipment/Instrument Installation | Mechanical | | X | X | | |
| Damage Instruments/Equipment | Mechanical | | X | X | | |
| Tagging and Labeling | Mechanical | | X | | | |
| Insulation/Caulking | HVAC/Mechanical | | X | X | | |
| Out of alignment structure steel | Structural | | | X | | |
| Stair Risers not to spec. | Structural | | | X | X | |
| Room Finishes | Structural | | X | X | | |
| Storage of Materials | Material Management | | X | X | | |
| Mold on Walls | Material Management | | X | X | X | |
| Cable Installation | Electrical | | X | X | | |

Table A. Additional types of issues identified during the construction phase by the CQM effort.

would have caused significant cost and schedule delays.

- Drywall Mud Application Temperature
  Specifications called for drywall mud to be applied between 13°C and 26°C. Actual application was occurring at 3.3°C. Mud was removed and reapplied at proper temperature - *Figure 6*.

- Leak Detection Level Switch
  A leak detection level switch was installed in the wrong nozzle of a sump - *Figure 6*. This issue would have been ultimately discovered; however, by detecting and resolving the problem early, it prevented the issue from surfacing in the commissioning/qualification phase and causing a potential schedule delay.

- Missing Pressure Indicator
  Typical of QOR issues was a missing instrument that the drawings had indicated, but had not been installed - *Figure 6*. The CQM group identified and quickly resolved the problem with sub-contractors and prevented the issue from surfacing in the commissioning/qualification phase and causing a potential schedule delay.

- Shaft Wall Construction
  Elevator, mechanical, and stair shafts were not being constructed per detail. The contractor had decided to construct them as they did on previous Lilly projects. The head design of these shaft walls were designed for specific load ratings unique to this project. After design review by the A&E, it was apparent that failure would have almost certainly occurred had the rework not been performed.

  All walls in place were repaired and the intended design was implemented on remaining walls. Miscommunication and incorrect assumptions can create confusion regarding specifications and expectations. This finding alone and its potential safety implications justified the entire CQM program on the project and reinforced the strong link between quality safety.

Additional types of issues identified during the construction phase by the CQM effort included the following:

### *Results*

The CQM manager and Lilly worked very closely throughout the project to manage quality with the construction manager and were able to have significant impact on the project. The premise of the effort was that improved construction quality would result in less construction related issues appearing during commissioning. As a result, the team responsible for executing the commissioning would be able to test and approve systems in a timely manner with fewer issues and deliver the facility to the customer on-time and at or below cost.

*Continued on page 70.*


Figure 6. Typical construction quality related issues.

As a result of applying the CQM Program, the following was observed:

- **14,921 Issues Identified**
  Each issue was catalogued in a database and tracked to closure by the CQM manager and the contractor. (See Figure 6 for typical construction quality related issues).

- **35.4% of Issues Identified were Potentially Commissioning Impacting**
  It was determined that 5,247 of the issues (35.4%) were determined to have potential impact on the ability to commission to facility.

- **2.0% Impacted Commissioning**
  A total of 303 items or 2.0% of all items were discovered in commissioning that could impact commissioning. Most of these items were minor and had minimal impact.

- **$2.8 Million Correction Pre-Commissioning**
  It was estimated that the cost of issues resolved prior to commissioning was conservatively around $3.0 million. These issues were identified by CQM manager and corrected/paid for by the contractor.

- **$380,000 Corrections during Commissioning**
  It was estimated that cost of issues resolved during commissioning was just under $400,000. These issues were identified by CQM manager and corrected/paid for by the contractor due to good tracking and issue resolution.

- **Contractors Retainage was Typically Paid Within 30 Days of Agreed Substantial Completion**
  Sub-contractors realized the management of quality throughout the project meant final closure and payment was more easily obtained.

The commissioning of the facility proceeded extremely well, coming in under budget, and meeting the timelines of the business owner. During the project, significant quality issues had been identified early and addressed in a timely manner. The contractor acknowledged to Eli Lilly management that without the CQM program it would have been impossible to deliver the project on-time and under budget.

### *Benefits*

Construction Quality Management needs to be a collaborative effort between the owner, designer, and construction teams. Clarity of expectations defined through accurate drawings and specifications is of paramount importance. However, good planning, communication, and proactive management of construction quality help establish a project execution focus and a "Right First Time" culture in the field.

The CQM approach outlined above was a minimal investment (i.e., 0.5% of Total Installed Cost, TIC) by the owner to assure field quality. The benefit achieved was a project delivered on time, under budget with quality issues addressed in a proactive, real-time manner, and paid for by the contractor; rather than have the issues surface during the commissioning/qualification phase or even later after transfer of custody to the owner.

Lilly has successfully used this approach with similar results on a manufacturing facility in Puerto Rico and has similar programs on-going with other capital projects in the United States, Ireland, and France.

### *Learnings*

In effectively implementing and managing the CQM program, the following important learning points were identified:

- **Real Time Management of Issues**
  It was important to identify and manage issues in a timely manner through regular meetings and this had the following impact:
  - reduced items at end of project
  - simplifies path to mechanical completion
  - allows to look for trends

- **Pre-Work Quality Meeting With Sub-Contractors Added Value**
  Meeting with the sub-contractors prior to beginning work, helped achieve the following:
  - verified that specifications were understood
  - assure training plans, inspection test plan, etc. were in place

- **CQM must be Managed**
  The CQM effort can be a cultural change and a challenge for contractors. It requires attention to detail, tracking of issues, and accountability. It requires focus and resources based on complexity of the project.

- **Field Inspection Reporting Program**
  A structured field inspection pro-

*Concludes on page 72.*

gram with scheduled and focused inspections by the inspection team and contractor is needed. This inspection program should include:
- engaged crafts people in identifying issues
- tracking program in place for issues

- **Metrics Provide Assessment Tool**
  Tracking metrics provide a mechanism for assessing program and providing timely feedback.

- **Effort must be Appropriately Scaled for Project**
  The level and degree of the CQM program can and must be scaled to the complexity of the project.

Finally, a member of the field execution team made the following statement,

***"Every time I walk on a job my eyes are wide open to "Safety" and now "Quality" as well. My experience on this project changed my mindset and awareness to the importance of construction quality."***

## Summary

Good construction quality is a prerequisite for successful commissioning and qualification. It is important to remember that "commissioning" is an iterative step that will help bring to life the ideas/concepts that were initially developed by the designers/engineers; and if executed properly, it can help successfully handover a facility from "field" to "operation and maintenance." "Qualification" on the other hand, is a step that will finally tell you what has "passed" and what has "failed," and one of its primary purposes is to facilitate regulatory compliance.

Typically, for $100 million (€100 million) Total Installed Cost (TIC) biotech facility, the commissioning and qualification costs (when utilizing a leveraged approach) would normally run anywhere between 2.5 to 5% of TIC, depending on complexity and level of sterility. However, in comparison, the construction quality management would typically run at around 0.5% to 1% of TIC. Therefore, a relatively small investment upfront in construction quality can bring huge benefits at the end of the project and beyond!

In reality, the true cost of failing to get your facility up and running on time is missing a launch date for a product or losing a race to market or not being able to maximize your revenue by not meeting market demand for a product.

## Conclusion

In conclusion, the selection of a good constructor is obviously very important; however, selecting a third party to perform CQM early on the project will have a very significant impact on the project outcome. A clear commissioning strategy, underpinned with a good CQM program, established at the preconstruction stage of the project, can help translate good engineering design into field execution/construction and help alleviate many of the problems encountered at the back end of a project. It also should give the overall project team a better chance of delivering the capital project on time, to budget, with good design, great quality, zero defects/accidents, good operability and maintainability, as well as high availability and reliability!

## About the Authors

**Jay Lad** is the Managing Director of SPGL (formerly the business of Skanska Pharmaceutical Group Ltd.), leading its construction quality, commissioning, qualification, and regulatory compliance services globally. He is a chartered chemical engineer with nearly 20 years of experience in the pharmaceutical and biotechnology industry, covering facility and process design, construction, commissioning, qualification, and project management. Lad has worked in a variety of sectors, including bulk, pharmaceutical, biotechnology, and medical devices and has considerable experience managing commissioning/qualification businesses in the pharmaceutical and biotechnology realm. He holds a BEng. in chemical engineering, graduating with honours, from the University of Bradford in the United Kingdom and he has previously worked for several EPC contractors, including Raytheon, AMEC, Washington Group International, and Skanska. He can be contacted by telephone: +44 (0) 7970-652-880, +44 (0) 20-7084-6873, or by email: jay.lad@spgl.eu.

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**Bruce Beck** is a Director at Eli Lilly and Company who has responsibility for leading the Global Facilities Delivery (GFD) Commissioning and Qualification group. This group has responsibility for assuring new facilities delivered by Lilly's GFD are properly commissioned and qualified. This group has established corporate C&Q procedures, standards, and methods used throughout the corporation for delivering capital projects and have been very successful in driving standardization and global improvement. Beck has a BS in chemistry and an MS in chemical engineering from Ohio State University. He has worked for Eli Lilly and Company for 28 years in a variety of roles, including technical services, manufacturing management, environmental, and health and safety management, and most recently over the last nine years has managed the Corporate Commissioning and Qualification group for Global Facilities Delivery. He can be contacted by telephone: 1-317-277-3413 or by email: beck_bruce_e@lilly.com.

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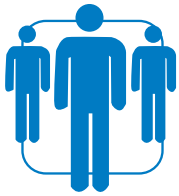

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# PQLI Update from Strasbourg

By Dr. Kate McCormick, ISPE European Education Advisor

Industry representatives and senior regulators attending the PQLI seminar in Strasbourg heard latest developments in ICH Q8(R1), Q9 and Q10 implementation.

Susanne Keitel of EDQM sounded a note of caution. QbD is an optional approach and companies may not wish to adopt it for their whole portfolio. A tiered system is therefore needed. Keitel confirmed that flexibility is already written into the European Pharmacopoeia and explained the new non-mandatory sections on FRCs had been added to monographs for information only. In conclusion, Keitel emphasised that whatever approach to development is chosen, safeguarding public health should be the first priority.

# ISPE Strasbourg Conference a Success

Pharmaceutical science and manufacturing industry professionals from around the world gathered in Strasbourg, France to share expertise and gain insight to "Managing Knowledge through Science and Risk Assessment" at the 2009 ISPE Strasbourg Conference.

500 industry specialists from manufacturing companies, suppliers, and regulatory agencies gathered 28 September through 1 October at the Palais de Congres to exchange knowledge and ideas during educational seminars, workshops, networking sessions, and hands-on training.

Delegates attending the "PQLI – Global Realization and Implementation of the ICH Quality Vision" session had the opportunity to hear from senior regulators and industry leaders about latest developments in the implementation of ICH Q8, Q9, and Q10. See related article "PQLI Update from Strasbourg" by Dr. Kate McCormick.

Technology also played a pivotal role in the event. For the first time in Europe, select educational sessions were recorded – thus allowing the knowledge and experiences of the event to reach a wider audience – and are now available as downloadable webinars at www.ISPE.org/onlinelearning. Recorded sessions include Biological Products Manufacturing Challenges – Now and in the Future; Business Excellence Concepts, Process Development Improvements; Occupational Exposure Issues with Large and Small Molecules; and Risk-based Implementation of Single-use Systems. In addition, many of the seminars made use of voting technology to poll delegates, getting instant feedback on a number of questions posed by the audience.

In addition, it was the first time ISPE and INTERPHEX partnered to host a European vendor exhibition and a variety of networking receptions that allowed exhibit attendees to engage and network with fellow seminar delegates, vendors, and colleagues.

There was a unique opportunity to hear presentations by regulators from all three ICH regions and by industry leaders following the ICH meeting in Yokahama in June 2009.

Jean Louis Robert of Laboratoires National de Santé in Luxembourg and Chair of the Implementation Working Group, explained their role: to compile and publish Q&As; to organize training; and to develop case studies and joint publications.

There are three key topics. QbD is being led by the US FDA. Pharmaceutical Quality Systems (PQS) is being led from Europe. Knowledge Management (KM) is being led from Japan. In each case, a senior regulator presented the current situation.

Georges France of Wyeth Europa, UK and Bob Baum of Pfizer, USA gave the industry perspective. They reviewed benefits of the QbD approach, but emphasised the need for a change in culture across industry.

There were presentations on specific case studies currently being developed. Bruce Davis of Global Consulting, UK described an Illustrative Example (IE), which will demonstrate practical implementation of QbD in manufacturing and beyond. See related online exclusive article "Industry Meets Regulators for PQLI Update in Strasbourg" by Dr. Kate McCormick.

Graham Cook of Wyeth Pharmaceuticals, UK presented details of the Mock S2 project for drug substances. The purpose is to exemplify application of enhanced QbD concepts to the development and manufacture of both a traditional small molecule and a monoclonal antibody. Delegates received 'hot off the press' feedback from the latest training workshop organized by the EMEA PAT team, in conjunction with EFPIA.

Keith Pugh of MHRA, UK and chair of the PAT team described six real case studies presented during the workshop and highlighted a number of observations arising from the case studies.

Speaking on behalf of EFPIA, Georges France said there are challenges both for development/manufacturing and for assessors/inspectors.

Yukio Hiyama of the National Institute of Health Sciences, Japan presented recent changes to the pharmaceutical regulations and challenges presented by implementation of ICH Q8(R1), 9, and 10.

Emer Cooke, International Liaison Officer, EMEA described the significant role played internationally by EMEA and progress against the long-term vision of creating synergies through communication, collaboration, and cooperation to support a global approach to authorization and supervision of medicines.

Interactive workshops allowed comment on, and contribution to, current PQLI activities. Each workshop was lead by an industry representative and a regulator. Feedback from all workshops was presented in plenary session on the second afternoon.

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# Introducing the 2009-2010 Board of Directors

The following pharmaceutical industry professionals have been elected to positions on the 2009-2010 ISPE International Board of Directors:

***Chair:*** **Alan Mac Neice,** Ireland

***Vice Chairman:*** **Andre Walker,** Director, Manufacturing Engineering, BiogenIdec Manufacturing ApS, Denmark

***Treasurer:*** **Dr. Arthur (Randy) Perez,** Executive Expert, IT Quality Assurance, Novartis Pharmaceuticals Corp., USA

***Secretary:*** **Dr. Charlotte Enghave Fruergaard,** Senior Consultant, Finished Product Department, NNE Pharmaplan, Denmark

## New Directors

Each to serve the Society for a two-year term beginning 10 November 2009.

**Antonio Buendia,** Project Engineering Manager, Lilly SA, Spain
**Winnie Cappucci,** Quality and Compliance Computer Validation Specialist, Bayer Healthcare, USA
**Damian Greene,** Director/Team Leader, API Operations Team, Pfizer Global Manufacturing, USA
**Doyle R. Johnson,** Consultant, CDI Life Sciences, USA
**Morten Stenkilde,** Quality Director, Novo Nordisk A/S, China
**Andrzej Szarmanski,** Quality Director, Polpharma SA, Poland

## Directors in Place

The following Directors were elected in 2008 to serve a two-year term.

**Joan Gore,** Manager, Clinical Trial Packaging and Support Services, Eli Lilly and Co., USA
**Tomiyasu Hirachi,** Representative Director and President, EEM Japan Co., Ltd., Japan
**Stephen Tyler,** Director of Strategic Quality and Technical Operations, Abbott Laboratories, USA
**Dr. Guy Wingate,** Quality Director, GlaxoSmithKline, United Kingdom

## Past Chairman

The Past Chairman automatically serves one additional year on the Board.

**Charles P. Hoiberg,** Executive Director, Pfizer Inc., USA

# ISPE Announces Availability of A-Mab Case Study

ISPE has announced a major extension of its Product Quality Lifecycle Implementation® (PQLI®) initiative further into biotechnology. This development comes after the decision of the CMC-Biotech Working Group consortium to provide their A-Mab case study to ISPE. The public availability of the final version of this case study was announced during the PQLI session entitled, "Regional Regulatory Experiences Implementing the ICH Quality Vision" held on 10 November, during the Society's Annual Meeting in San Diego, California, USA.

"This marks a significant opportunity for PQLI," said ISPE President and CEO Robert P. Best. "We can now provide even greater support to the biotechnology community in the implementation of the advanced concepts of Quality by Design. We have plans to use it extensively around the world in discussions with industry and regulators throughout 2010 and beyond."

The CMC-BWG consortium comprises some 40 members from seven companies (Abbott, Amgen, Genentech, GlaxoSmithKline, Lilly, Medimmune, and Pfizer) and was established in 2008 to develop a case study illustrating how the principles of Quality by Design (QbD) can be applied to the development of biotechnology products, focusing on monoclonal antibodies. The A-Mab case study discusses the development of a monoclonal antibody and incorporates many advanced and aspirational QbD concepts.

"The CMC-BWG team has created an amazing and unique case study that is generating intense interest and excitement among the Industry and Regulatory Agencies around the world," said ISPE PQLI Project Manager, John Berridge, who served as one of the facilitators for A-Mab. "Many have questioned whether the principles of QbD are applicable to biotechnology. A-Mab answers that question with a resounding 'yes.' The mission was to describe a future state based on new ways of thinking and A-Mab definitely challenges the sometimes conservative ways industry does things today. We were constantly pushing the envelope to capture an aspirational QbD state showing enhanced product and process understanding. This is not a mock submission seeking regulatory approval. A-Mab provides many illustrative, sometimes controversial, examples of ways to implement QbD and will stimulate discussion about how the science supports these examples and how we can enhance future biotechnology product realization. This is an exciting 'next step' in the biotechnology work of PQLI."

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## 2010 Tampa Conference

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## 2010 Milan Congress

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Milan, ITALY

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Hach Co., 5600 Lindbergh Dr., Loveland, CO 80539. (970) 663-1377. See our ad in this issue.

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ISPE ENGINEERING PHARMACEUTICAL INNOVATION

# Latest Baseline® Guide Reviewed by the FDA Focuses on OSD Manufacturing Design and Construction


The newly released *Oral Solid Dosage Forms Baseline® Guide* addresses the latest interpretation of GMP requirements, as well as a risk-based approach to regulatory compliance relating to the design, construction, and validation of the OSD manufacturing facility.

This second edition is a revision of the original *Oral Solid Dosage Forms Baseline® Guide* published in February 1998. The revision includes an expanded product and processing chapter with detailed discussion of each critical unit operation and new technological trends, such as continuous processing and implementation of process analytical technology. The Guide provides a comprehensive view of best practices available in the pharmaceutical industry for oral solid dosage manufacturing facility design and construction. A lifecycle approach to project management is emphasized.

The following is the Table of Contents:

- Introduction
- Concepts and Regulatory Philosophy
- Product Protection
- Product and Processing
- Architectural
- Process Support and Utilities
- HVAC
- Electrical
- Control and Instrumentation
- Other Considerations
- Risk-Based Approaches to Commissioning and Qualification
- Appendix 1 – Cost Factors in OSD Manufacturing
- Appendix 2 – Summary of Quality Risk Management Process
- Appendix 3 – Risk Management Tools
- Appendix 4 – HSE International Regulations and Standards Cross References
- Appendix 5 – References
- Appendix 6 – Glossary PE

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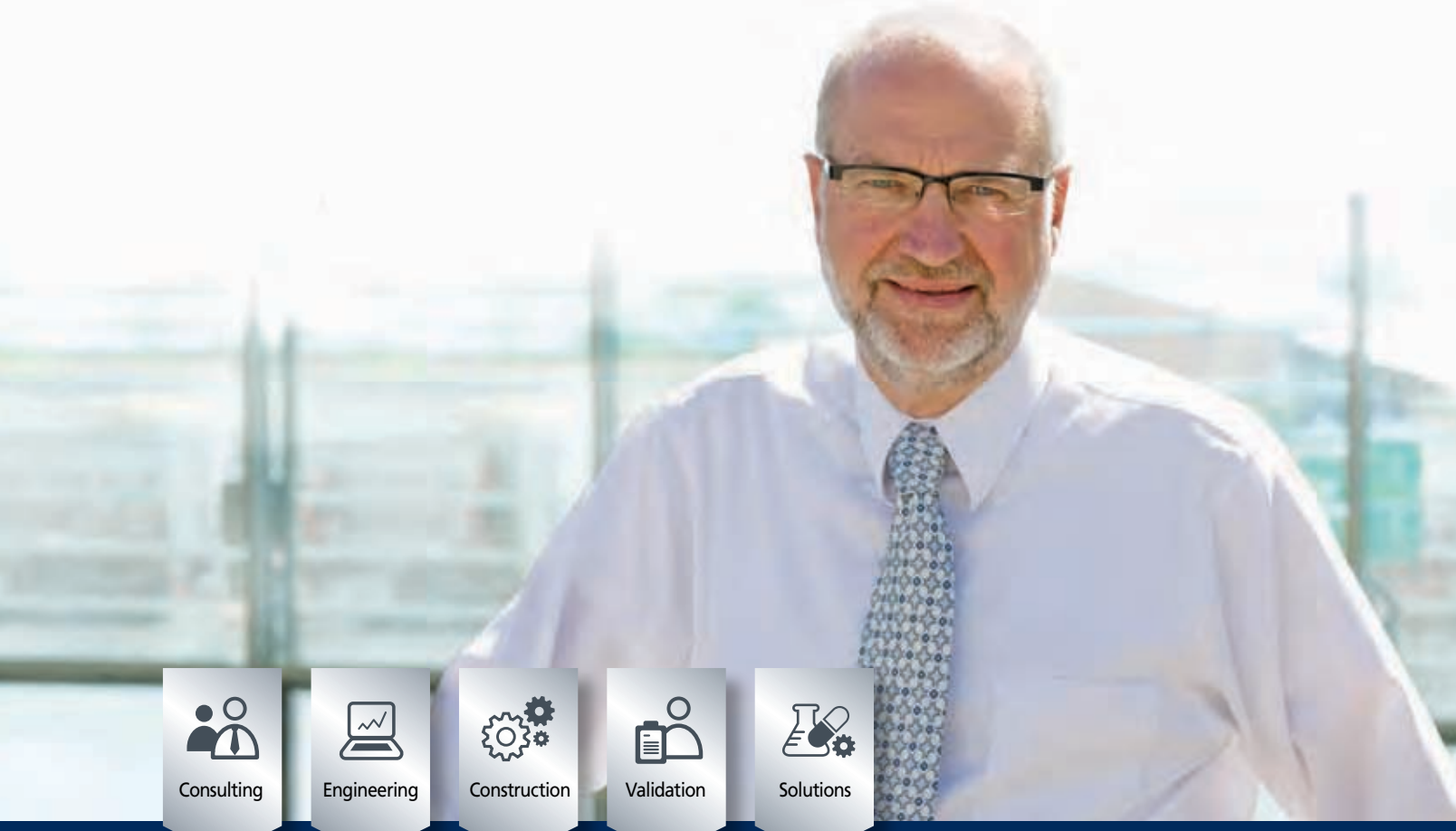

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**This article presents a practical application of Quality Risk Management for the extent of verification necessary during Factory Acceptance Testing (FAT), Commissioning and Qualification (C&Q).**

# Applying Quality Risk Management Principles to Achieve a Practical Verification Strategy

by Ian Campbell

## Introduction

This article provides the optimum requirements for Factory Acceptance Testing (FAT) and Commissioning and Qualification (C&Q) of equipment for compliance with current Good Manufacturing Practices (cGMPs) as mandated by the US Food and Drug Administration (FDA), EMEA, and Health Canada. The requirements also are consistent with the International Conference on Harmonization (ICH) Guidelines.

A Quality Risk Management (QRM) approach to verification focuses on critical attributes of the equipment as they relate to product performance and their relevance to quality, strength, purity, safety, and efficacy. The strategy is based on the degree of comprehension of the manufacturing controls and quality systems. This will allow for fewer restrictions when purchasing new equipment.

Three levels of risk classification are outlined in this article, which have been aligned with GAMP® 5 classification (high, medium, and low) applying the principles of Failure Mode and Effects Analysis (FMEA), where severity, likelihood of occurrence, and detectibility are quantified to evaluate the overall risk. All equipment can then be categorized based on criticality. General verification requirements were established to serve as a guide.

The assessment of equipment criticality or risks classification determines the requirements for verification and at what step in the procurement process they should be done, i.e., FAT versus commissioning versus qualification; depending upon the risk category assigned.

The focus of effort is then placed on verifying the most critical parameters to demonstrate that the equipment is under adequate control for the critical process parameters. New equipment will be assessed using this tool and the appropriate actions will be taken to ensure efficient compliance.

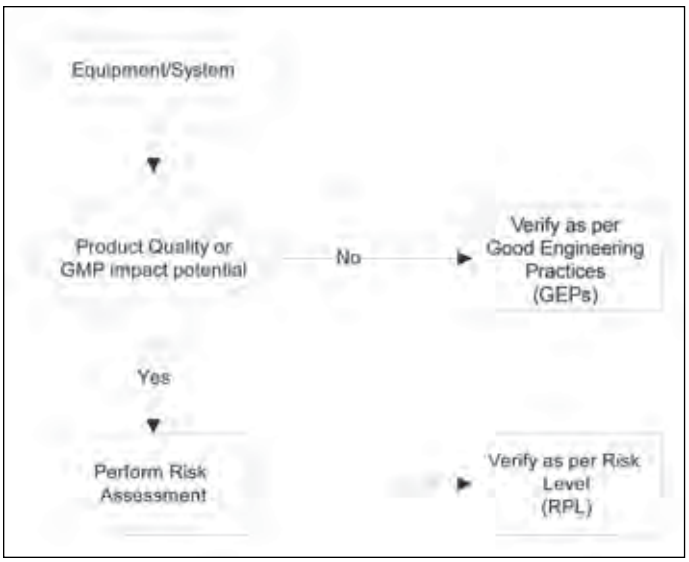


Figure 1. The assessment was based on quality and GMP risk. Any risk for disruption of business will be factored in as a discretionary decision as to the level of documentation required and should otherwise be based primarily on good engineering practices.

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## Strategy

The implementation of the QRM framework requires an educated, well-trained, and integrated team of Subject Matter Experts (SMEs). Expert opinions from engineering, operations (manufacturing), validation, and quality operations were used to assess the appropriate critical to quality risk indicators and to assign the risk levels.

All equipment is first assessed and evaluated against the supporting cGMP systems in place, such as the necessary maintenance, calibration routine, procedural

*Continued on page 18.*

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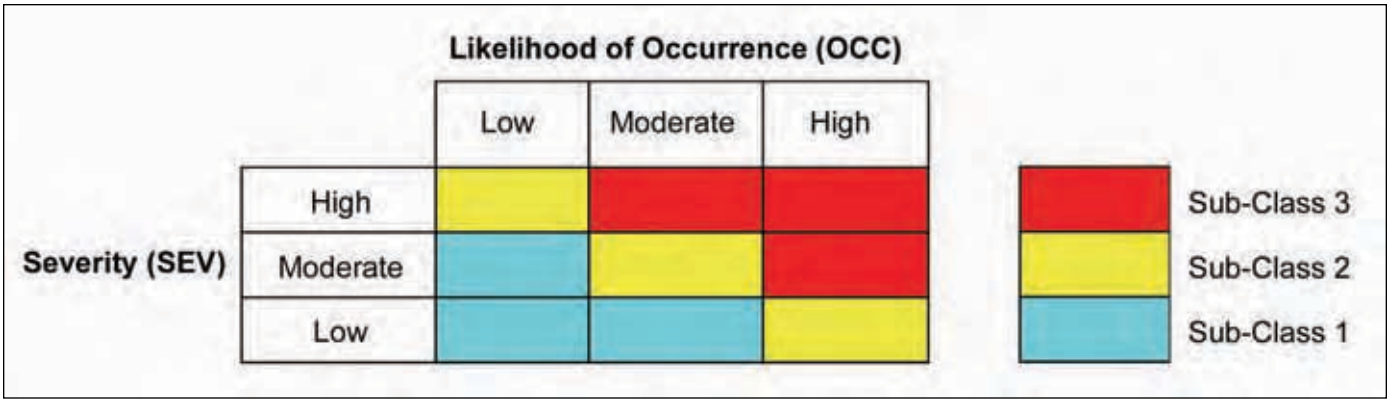


Figure 2. "Severity" (SEV) vs. "Occurrence" (OCC) to obtain "Sub-Class."

controls, etc. These cGMP systems enable a continued support to the initial and continued state of qualification/verification. All available information and data is formulated to estimate the probability of the worst possible problem (failure) occurring. A further assessment is then performed to characterize the risk and establish a guideline for a verification plan.

A three step process is undertaken to determine the necessary verification activities and when they can be performed.

## Categorization of Equipment

The equipment is first evaluated based on the complexity of operations and the critical parameters to which they are subjected. Although the systematic evaluation of risk should be as exhaustive as possible, additional observations may be added where appropriate, in order to accommodate specific equipment or compliance requirements.

The equipment should be separated into categories or types based on unit of operation. The categorization is done based on operating principles and design characteristics. In some cases, the particularities of the unit operation within a given equipment category may require further division into subclasses. For example, a balance used to weigh loaded pallets prior to shipping should be treated differently (separated into a different category) than an analytical balance used to dispense raw materials to be processed in a batch of drug product.

## GMP Impact Assessments

Each category of equipment should then be evaluated against specific, pre-established criteria to determine if the equipment or any part of it could potentially impact the quality of product or patient safety and hence, impact cGMPs. If the impact assessment determines that there was no potential for the equipment to impact product quality or GMPs, the equipment is not evaluated further, but falls under the scope of Good Engineering Practices and verifications required for non-GMP purposes.

Any equipment that is judged to have a potential impact on the product or GMPs should undergo a risk analysis to determine the associated level of risk. A thorough analysis of the operating principles and design characteristics of each equipment is performed by a team of highly trained, professional Subject Matter Experts (SMEs) in order to determine the worst potential failure of that category of equipment. The worst case failure can be evaluated using the GAMP 5[1] model of FMEA. The necessary verification requirements can then be determined with the level of risk.

## Risk Assessment

A Risk Priority Number (RPN) is established based on the overall risk of failure as indicated by the likelihood of occurrence, detectibility, and severity. Equipment should be ranked based on the potential risk of failure as it translates to the end user (or patient) by an erroneous result. Different categories

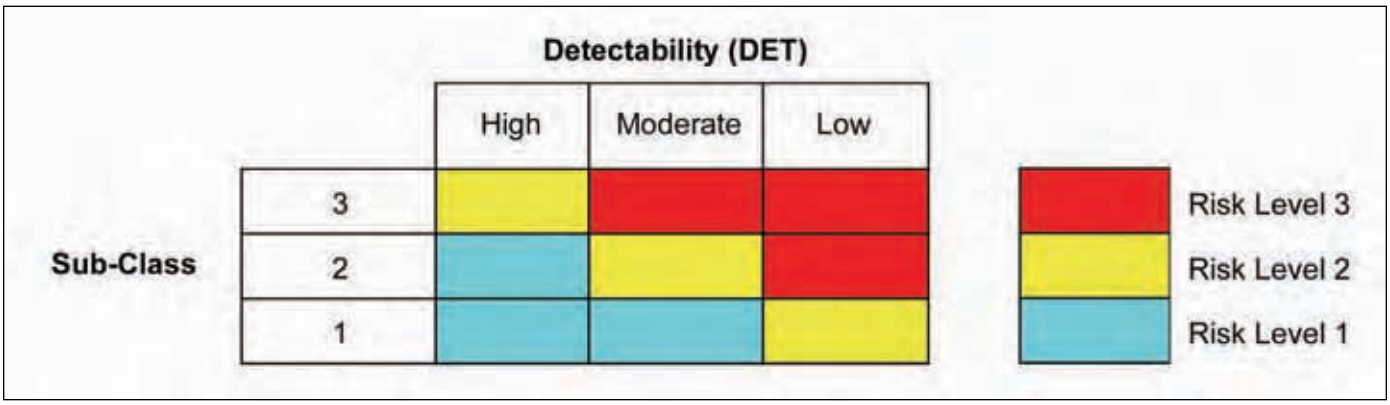


Figure 3. "Sub-Class" vs. "Detectability" (DET) to obtain "Level of Priority." Reference ISPE GAMP 5 (Adaptation).

*Continued on page 20.*

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| Risk Level | FAT Requirements | Commissioning Requirements | Post Commissioning Installation Verification | Post Commissioning Operation Verification |
|---|---|---|---|---|
| 3 | • Ensure equipment meets design specifications as per User Requirements Specifications (URS) and Purchase Order (PO).<br>• Define and perform extensive operational testing as per URS.<br>• Run simulation of actual application if possible. | • Verify that the equipment has been entered in the site systems.<br>• Perform operational tests as outlined in the URS.<br>• Perform extensive testing simulating actual application. | • Verify that commissioning tests were completed as required.<br>• Verify that necessary systems are in place.<br>• Verify specific items as indicated. | • Testing of primary equipment functions as defined in the URS.<br>• Testing of equipment auxiliary functions, due to their complexity and their direct impact on product quality.<br>• Verify that commissioning tests were completed as required. |
| 2 | • Ensure equipment meets design specifications as per URS and PO.<br>• Define the necessary operational tests as outlined in URS. | • Verify that the equipment has been entered in the site systems.<br>• Perform operational tests as outlined in the URS. | • Verify that commissioning tests were completed as required.<br>• Verify that necessary systems are in place. | • Testing of primary equipment functions as defined in the URS. Note: It is necessary to document a rational for testing or not testing certain functions.<br>• Verify that commissioning tests were completed as required. |
| 1 | • Ensure equipment meets design specifications as per URS and PO. | • Verify that the equipment has been entered in the site systems. | • Verify that commissioning tests were completed as required. | • Verify that commissioning tests were completed as required. |

Table A. Overview of verifications per level of risk.

of risk should be aligned with FMEA principles using the risk assessment method outlined in GAMP 5 to provide for a systematic evaluation.

Each risk evaluated is meant to represent the highest overall risk potential for any failure that may occur. Each risk component was evaluated as outlined in the GAMP 5 risk assessment method in order to establish its likelihood of occurrence, severity, and detectibility. These categories are

| Test | Factory Acceptance Test (FAT) | Commissioning (COM) | Equipment Validation (VAL) |
|---|---|---|---|
| Equipment Identification | Verify | Verify | Refer |
| Product Contact Parts Verification | Define | Document | Verify |
| Equipment and Major Component Verification | Define | Verify | Refer |
| Visual Inspection | Verify | Verify | Verify |
| Company Specific Requirements | Fine Tune | Verify | Refer |
| Space Allocation | Define | Verify | Refer |
| Environmental Conditions | Define | Verify | Refer |
| Documentation Availability | Verify | Verify | Refer |
| Drawings, P&ID, etc. | Define | Verify | Refer |
| Purchase Order | Define | Verify | Refer |
| Computer/Automation Requirements | Define | Document | Verify |
| Access Level Verification | Define | Fine Tune | Verify |
| Input and Output Verification | Verify All Critical | Verify Representative% | Refer |
| Control Switches Operation Verification | Verify | Verify | Refer |
| Alarms and Interlocks Verification | Verify All Critical | Verify Representative% | Refer |
| Backup of the Application Software Verification | Draft | Fine Tune | Verify |
| Electronic Signature Verification | Define | Fine Tune | Verify |
| Electronic Record Verification | Define | Fine Tune | Verify |
| Equipment Safety Features Verification | Define | Fine Tune | Verify |
| Equipment Utilities Verification | Define | Verify | Refer |
| Power Failure Recovery/Surge Verification | Define | Verify | Refer |
| Equipment Preventive Maintenance Verification | Define | Fine Tune | Verify |
| Standard Operating Procedures Verification | Draft | Fine Tune | Verify |
| Radio Frequency Interference (RFI) | Define | Fine Tune | Verify |
| Instrument Calibration Verification | Define | Calibrate | Verify |
| Reject System and Fail Safe Verification | Define | Fine Tune | Verify |
| Functionality Testing | Verify Representative% of Functionality Tests | Verify Representative% of Functionality Tests | Functionality AQL – 100% |
| Performance Testing (where required) | Define | Fine Tune | PQ or Demo Verify |

Table B. Timing of verification.

then factored together to provide an indication of the overall risk as defined by the Risk Priority Number (RPN).

The RPN is then used to determine the required level of effort involved in the equipment FAT, Commissioning and Qualification. The equipment is then classified into three different categories based on their associated level of risk. This granularity will serve to ease the decision making process for the required level of qualification to be applied to any equipment. This approach is intended to serve as a guide and may be adjusted if required to suit any particular characteristic of a given piece of equipment. The categorization of the equipment allows us to determine the scope and extent of verification required as well as any other deliverables judged necessary.

Risk Priority Numbers (RPNs) for risk classification by levels of criticality are assigned for each equipment type based on several factors which include, but are not limited to:

- the degree of operational understanding or history
- the relative robustness of supporting systems
- the relative robustness of the process controls
- the relative complexity of equipment
- degree of variability of the equipment and controls used to detect variability

The RPNs are established for worst case failure that could potentially impact the strength, safety, purity, quality, and identity of the product. Considerations should be given to many of the supporting systems that serve as indicators of control, such as in process checks, calibration requirements, re-qualifications etc., as well as experience in using a given type of equipment, and any trends evident from investigation reports.

The severity of a given failure in relation to potential impact to product quality and GMPs is evaluated by the multidisciplinary team classified as high, medium, or low. The likelihood of occurrence for the given failure is then evaluated as high, medium, or low. The severity is compared against the likelihood of occurrence to determine the subclass of risk - *Figure 2*. This value is subsequently used to compare against the detectibility of the event in order to determine the overall risk associated with the failure.

The subclass determined from the previous step is then compared to the detectibility to determine the overall level of risk for the worst case failure. The associated level of risk is then ranked as a Risk Priority Level (RPL) as either low (1), moderate (2), or high (3).The risk levels are related to the impact on product quality and GMPs - *Figure 3*.

## Risk Priority Number (RPN)

### *Risk Level 3 – Highest Risk*

Equipment that generally have direct impact on product quality and/or GMPs are considered the highest risk. These are representative of the most complex equipment used. All Level 3 equipment will require an extensive verification, encompassing the entire range of operating parameters required for equipment use. The particular requirements and deliverables are outlined in Table A.

### *Risk Level 2 – Moderate Risk*

Equipment that generally have indirect impact on product quality and/or GMPs are considered moderate risk. These are representative of the moderately complex equipment used in the manufacture, packaging, or holding of drug products. Level 2 equipment require a less extensive verification and number of deliverables. The particular requirements and deliverables are outlined in Table A.

### *Risk Level 1 – Low Risk*

Equipment that have negligible impact on product quality and/or GMPs are considered low risk. These equipment are generally not the most complex used in the manufacturing, packing, or holding of drug product. Category 1 equipment will require a less extensive qualification study and number of deliverables. The particular qualification requirements and deliverables for category 1 processes are outlined in Table A. Control is ensured primarily through routine procedural controls as well as the normal supporting systems, e.g., calibration and Project Management.

## Verification

A comprehensive list of verifications to be undertaken is then created to ensure that the necessary controls are in place to maintain the quality, purity, identity, strength, and safety of our drug products and to respect all regulatory requirements. This is confirmed through the necessary approval of

*Concludes on page 22.*

*"The main objective of equipment verification is a reduction in variability through equipment and process understanding … QRM provides an effective approach to establish a scientific basis for the required verification effort."*

documents outlining the acceptance criteria approved by the required SMEs and quality unit for any system containing critical to quality aspects.

The necessary verifications and the level of detail required are determined based on the Risk Priority Number (RPN). The timing of each verification is then established so as to ensure resource optimization and to avoid unnecessary duplication. An outline of the recommended timing of activities that must be verified is presented in Table B. This list is not meant to be restrictive and should be evaluated throughout the project lifecycle.

## Conclusion

A systematic approach to verification through the application of QRM principles enables pharmaceutical manufacturers to apply an efficient approach to compliance in an increasingly complex manufacturing environment. The application of QRM principles as outlined in this article will allow for there to be a maximum compliance level by focusing verification on the critical to quality attributes with the most efficient use of resource through a systematic and scientifically sound approach.

The main objective of equipment verification is a reduction in variability through equipment and process understanding (e.g., application of knowledge throughout the equipment lifecycle). QRM provides an effective approach to establish a scientific basis for the required verification effort.

Application of this enhanced science and engineering knowledge in decision-making will improve the efficiency and effectiveness of the verification effort, allowing manufacturers to use valuable resources in a more efficient manner.

The approach outlined in this article will allow for much efficiency to be realized through a standardized process of performing the appropriate test at the appropriate time eliminating any unnecessary duplication. The primary focus remains the same: to assure the maximum amount of control over pharmaceutical product manufacturing and packaging operations.

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**This article discusses why Construction Quality Management (CQM) is the key to delivering successful capital projects and outlines some of the challenges encountered from a construction/ field execution perspective, rather than design/ engineering perspective. It highlights the pivotal role of CQM in ensuring that a facility has good operability and availability as well as high reliability and maintainability.**

# Construction Quality: the Key to Successful Capital Projects Delivery

by Jay Lad and Bruce Beck

## Introduction

What is deemed a successful capital project? Is it one which is built on time, within budget, in a safe manner with good design and great quality?

Many, in short, would answer yes. However, the true success of a project should be judged on how well the facility performs from an operability, availability, reliability, and maintainability perspective. This is the real test on how good a facility has been designed and built! Therefore:

***A successful project is where a facility reaches optimal operation, in a safe manner, and in the shortest possible time-frame, generating cash at the earliest possible opportunity.***

***A successful project is where a facility achieves a high availability and reliability during the first-cycle operation, maximizing cash flow through the first-cycle operation.***

## Background

The life sciences sector, predominantly a regulated industry, is well served from a design/ engineering perspective. It has many design guides readily available, such as the ISPE Baseline® Guides and GAMP®, ASTM E2500, etc. Designing quality into a facility has become the standard and the norm for biopharmaceutical facilities. Also, the culture of Good Engineering Practice (GEP) and Good Documentation Practice (GDP) is a well established concept across many market and industrial sectors.

However, a well designed facility with excellent quality and specification has little or no value if the design is not properly translated into the construction and start-up of the facility. There are many different delivery methods for capital projects; however, all approaches tend to involve taking a design, breaking it down into manageable packages, and sub-contracting the work packages in a manner which will allow the constructor to reduce his risks and make a reasonable fee on the project. Therefore, a constructor does not really build a facility; he simply selects and manages sub-contractors.

***Therefore, the facility one builds is as good as the selection and management of the sub-contractors!***

In general, biopharmaceutical facility design/ construction is an "evolving/changing" world. It is a world where ideas, concepts, and designs are developed by engineers/scientists and which constructors attempt to bring to reality. Often, at the design phase of a project, the products are still in the development phase and yet to be fully characterized and understood. As a result, aspects of the facility often evolve and change during the design and construction phases of the project. In some extreme cases, the facility can be completely redesigned mid way through a project.

However, in stark contrast, the world of pharmaceutical manufacturing is a "precise" world, heavily scrutinized and under strict Quality Assurance/Quality Control (QA/QC) control. It can be characterized by its "batch sheet" mentality.

For a long time, engineering groups have been trying to apply the batch sheet mindset to the evolving/changing world of engineering and construction, often resulting in escalating costs and large program over-runs/delays.

The biopharmaceutical industry is very competent in the QA/QC of its manufacturing processes, but struggles to extend this competency in quality to the delivery of capital

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projects. Delivery of capital projects and construction quality are not always the core competencies of the owners; however, it is extremely important to a successful project.

Construction companies tend to be field execution driven with their focus on safety. Ideally, safety and quality should be combined to deliver projects with zero accidents and zero defects/punch lists. Using industry standards, such as ISO9000, can assure that construction companies have fundamentally sound management practices and a foundation for quality.

At the outset of a project, the appropriate level of quality must be determined for all phases of the project. This is usually established for the engineering and the qualification phases of the project. However, it is usually overlooked for the construction and commissioning phases of the project, probably the two most critical phases of the project that impact operability, availability, reliability, and maintainability of a facility.


Figure 1. Commissioning flowchart.

*Continued on page 62.*

At the start of a project, the start date and end dates are usually set in stone and it is usual for the design, engineering, and construction phases of the project to over-run. However, there is not much room for the commissioning phase of the project to over-run, as it is the penultimate phase of the project, prior to qualification and handover to the client. It also is one of the most critical and hazardous phases of the project, largely due to the fact that systems are energized and started-up.

A good constructor should normally have a commissioning plan developed at the pre-construction stage of a project. The objective being that the most critical and dangerous parts of the project is fully mapped out and costed, even before the construction has started. (See Figure 1 for an approach to commissioning).

However, a well planned commissioning program with excellent protocols and check sheets is of no value if the construction of the overall facility is of a poor quality and littered with defects. Therefore, the overall commissioning effort will ultimately prove to be more hazardous, troublesome, and costly.

It is clear from the above that at the pre-construction stage of the project, the approach to construction quality should be fully established in a construction quality plan. The level of quality to be applied to the project should be clearly laid out and fully understood by all parties.

The term "quality" in the life sciences industry has significant connotation and emphasis as absolutely central to the mission of the business. The concept of quality also has importance in the construction industry, especially in the delivery of new or modified biopharmaceutical facilities. The type of quality issues addressed during the construction phase may range from potential product quality impacting issues to more commonly quality deficiencies that are an operational and/or maintenance type issue (e.g., heat tracing for external piping not installed properly, resulting in frozen pipe work during extreme cold weather conditions). These types of quality issues are often a nuisance and costly to address after construction handover. They also can hinder operability, availability, and reliability of facilities.

Establishing a culture of quality within an organization is not something that can be implemented quickly. It requires a complete turnaround in corporate culture and management approach as compared to the traditional way of top management giving orders and employees merely obeying them. It's also a slow and gradual process, which requires substantial investment and commitment, which may not always make commercial sense in the construction industry. The main two factors which may cause this are highlighted below:

- **Product Diversity**
  All buildings/facilities are unique. Quality is seen as consisting of those features, which meet the specific needs of an industry, market sector, or customer and thereby provide satisfaction, supplemented with a proviso of freedom from defects.
- **Organizational Stability**
  The construction industry has a high number of collapses, especially during a downturn in the economy. Thus, commitment toward quality strategies and policies that may take several years to provide "pay offs" may be perceived as futile or a misdirection of resources. As compared to the head office, the construction site is transitory. Teams specially formed for a project may cease to exist after contractual obligations end. Add to this the fact that the implementation of quality in construction requires the selection of the appropriate sub-contractors who would commit to the quality process and develop a true quality attitude.

From the above, it would appear logical in some instances to have the construction quality function managed by a third party; one who really understands field execution, safety, and can bring the appropriate level of quality to the field game of construction.

Figure 2. Integrated Commissioning and Qualification (ICQ) flowchart.

Is it the architect, engineer, or would it make more sense to have a commissioning firm work closely with the construction company to integrate quality into construction and hence leveraging this into commissioning and qualification. (See Figure 2 for an integrated approach to commissioning and qualification).

A commissioning firm which understands field safety, construction quality, and qualification requirements may be ideally placed to take on the role of "Construction Quality Management (CQM)." If executed properly, not only can this role be carried out in a cost effective and independent manner, but also add great value to both the constructor and the end client.

So how can a commissioning company deliver the right quality to the construction activities in the field? This can be achieved by adapting the principles of Good Engineering Practice and Good Documentation Practice to suit construction.

This section outlines the general process that could be employed in the execution of quality management of construction projects. The program should be tailored for each project to ensure proper levels of continuing quality are achieved. The program should form the basis of, and should be a prerequisite to successful commissioning and qualification.

## Construction Quality Management (CQM) Program

The Construction Quality Management (CQM) program is the enabling process that allows clients to use other construction contractors with varying levels of regulated industry project expertise, yet be assured that the outcome is a trouble-free commissioning, qualification, and validation execution ensuring a reduced time to market.

The overall approach is to apply quality concepts and practices to the construction activities to ensure that the facility is delivered on time, as specified, defect free and in an operable state. One of the primary objectives of the CQM Program is to raise the importance of "quality" and "self inspections" to the constructor/sub-contractors in order to prevent deficiencies, minimize defective work, and strive toward a zero critical items punch list.

Ultimately, a facility with a good construction quality program and minimal defects is more likely to have a smooth and trouble free transition into the commissioning/qualification phase of the project.

The CQM Program should ensure proper construction turnover and that systems are ready for commissioning. For GMP critical systems, enhanced commissioning should then be performed to ensure that commissioning activities and documentation can be leveraged into qualification, hence, reducing time-to-market.

The level of quality for any project is defined by the contract requirements, drawings, specifications, current Good Manufacturing Practices (cGMP) and approved quality assurance/quality

*Continued on page 64.*

control guidelines.

As the design begins to crystallize during the development stage, the CQM Manager in conjunction with the client should begin to develop a project specific Construction Quality Plan, documenting the key steps it will take to deliver a building/facility that is fit for purpose. It is crucial to establish clear goals and objectives for the project, which will establish an appropriate level of quality expectations. As soon as the goals are set, the CQM Manager should develop a detailed Construction Quality Plan encompassing:

- Roles and Responsibilities
- Submittal Quality Management
- Subcontractor Quality Management
- Definition of Required Turn-Over Documentation
- Material and Field Quality Management
- Discrepancy Management and Control
- Training of Client personnel
- Hand-Over to Client

In order to effectively manage and execute the construction quality, the Construction Quality Plan needs to be part of an overall CQM Program. The CQM Program should form the basis for integrating construction with commissioning. The aim of the CQM Program is to reduce cost and time to market through a number of critical steps as identified below - *Figures 3 and 4*.

### *1. Risk Assessment and Criticality Analysis*

At the start of a project, it is important to identify and understand critical aspects of the entire project that will impact schedule and cost.

Currently, risk analysis is carried out at the design phase of a project, by the engineers and end users, usually from a design and engineering perspective. The result normally captures the client's expectations by classifying systems into critical/direct impact systems and non-critical/indirect impact systems. This is obviously significant because critical systems, or higher risk systems, require a higher level of documentation and field inspections.

However, it is just as important to identify and assess the risks to the project from a field execution perspective. Therefore, at the pre-construction stage, the risk assessments also should be carried out from a field perspective, identifying/assessing the criticality and interdependencies of systems, not just from a quality perspective, but also from a schedule impact perspective. This should apply to all systems, not just GMP impacting systems, and should be carried out by the CQM manager, constructor, and the client. A risk assessment, which is executed from both a "quality" and "schedule" perspective, will allow the field team to focus with the end in mind.

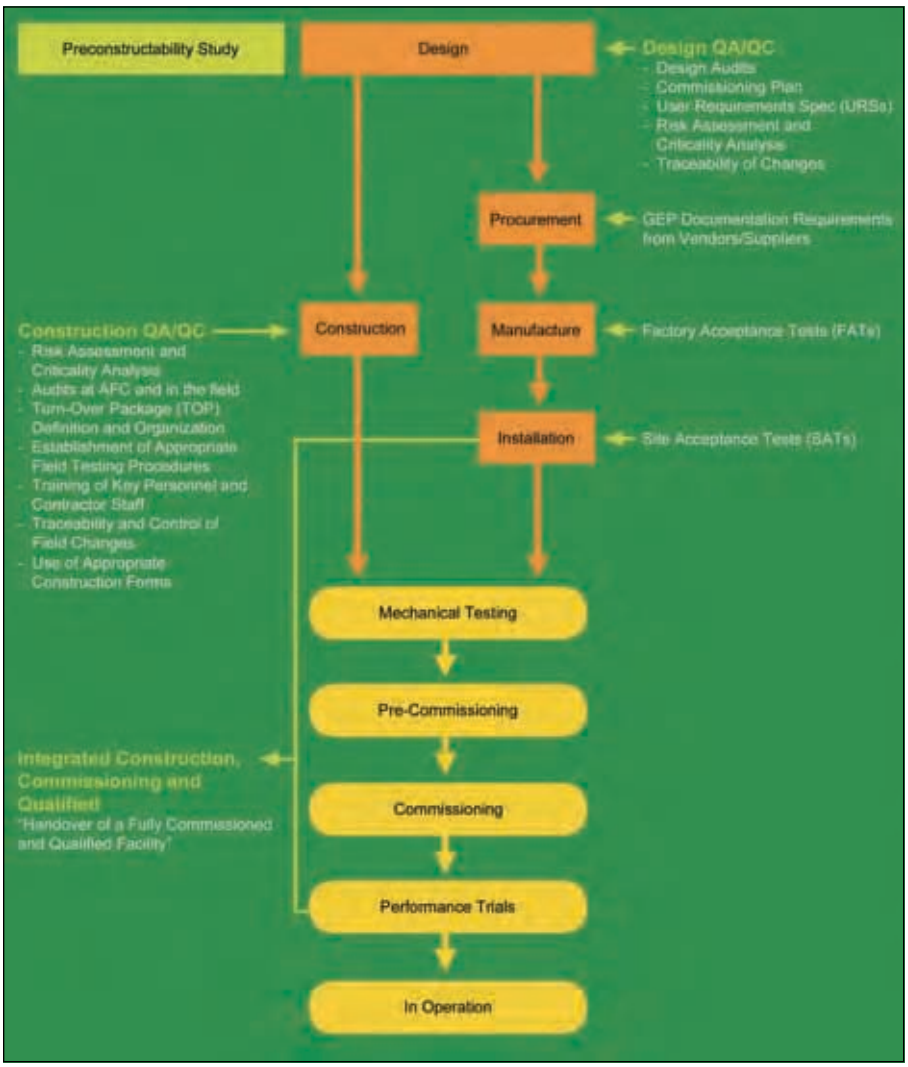


Figure 3. Approach to project quality.

### *2. Audits for Approved for Construction (AFC) Drawings and in the Field*

Compliance audits are normally carried out at the design phase of a project, by the engineers and end users, usually from a GMP/GEP perspective. The result normally captures a lot of potential issues, largely from a regulatory, operability, and maintainability perspective. However, often little or no auditing is carried out from a construction/field execution perspective.

The CQM manager should perform field audits, focused on high risk/critical systems that have been identified during the risk and criticality analysis. The primary objective of the field audits should be to highlight construction quality issues that may impact start-up/commissioning, and hence, the overall project schedule. The field auditing should be supported by a formal process

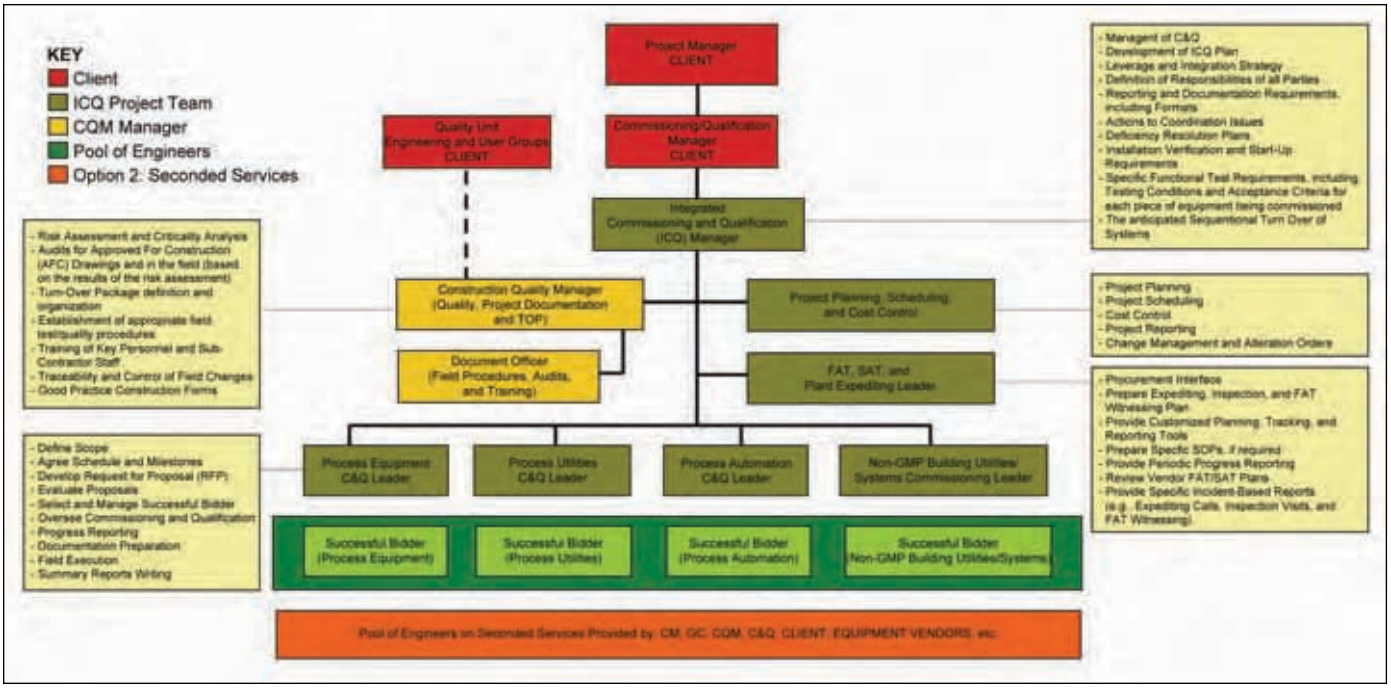


Figure 4. Project execution organization.

to record, manage, and resolve issues.

Ideally, the CQM manager also should perform compliance audits on "Approved for Construction" documentation prior to start of work as well as review bid packages to assure that the requirements of the operating company are included and delivered. This is applicable to both vendors and sub-contractors. Regular

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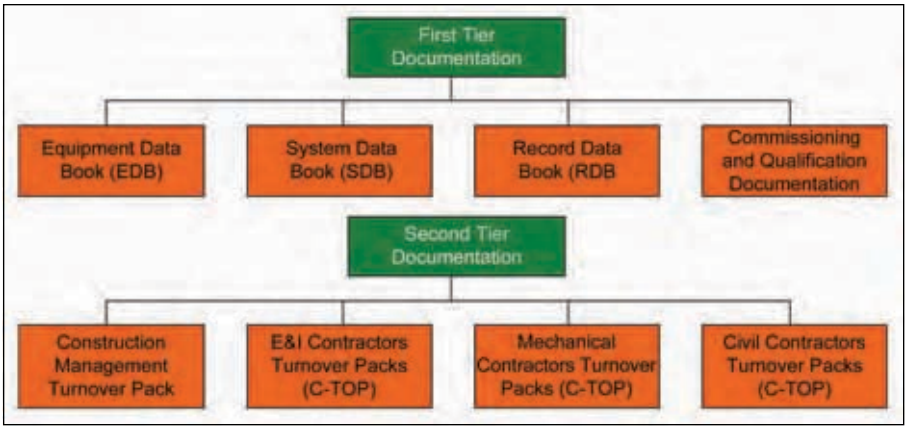


Figure 5. Turn-Over Package (TOP) organization.

meetings should be held with vendors/sub-contractors in order to ensure that specifications are understood and appropriate procedures are in place.

### 3. Turn-Over Package (TOP) Definition and Organization

The CQM manager should develop the Turn-Over Package (TOP) procedure, ideally at the preconstruction stage of the project. This procedure should be discussed and agreed with the constructor and sub-contractors as they will ultimately be responsible for assembling the TOPs. The CQM manager should audit the development of the TOPs and conduct a final review at hand-over stage. This should guarantee a high quality package, which should include all required up to date documentation from vendors, engineering, CM field activities, procurements, etc.

The organization of the TOP is extremely critical to the success of the qualification process; therefore, it must be structured and indexed in such a way that the client is able to leverage the documentation and data into qualification.

However, the TOP also is critical from an operation and maintenance perspective. Once the facility has been completed, the commissioning and qualification documentation will certainly support the regulatory effort. However, a good TOP also should consider how the facility will be operated and maintained after hand-over and what documentation will be required to achieve this. Figure 5, illustrates a two tier TOP architecture. The first tier documents are those deemed to be critical to plant operation, commissioning and qualification. The second tier documents are largely those documents that will be referenced by the first tier documents.

- Tier 1: Equipment Data Book (EDB)
  The EDB should provide plant engineers, supervisors, and maintenance personnel with an accurate reference file for maintaining the plant equipment to the optimum performance level. These files should contain all information relevant to a piece of equipment grouped by area and purchase order. The bulk of this information should be made up from vendor supplied documentation.

- Tier 1: System Data Book (SDB)
  The SDB should provide information to a particular part of the plant set by system boundaries. The SDB should aid plant engineers, supervisors, and maintenance personnel with an accurate reference to the location of equipment, instruments, system boundaries, etc. for maintaining the plant equipment to the optimum performance level. Where documentation is not inserted in the SDB, but required for the system, reference should be made to the documents location, i.e., equipment data files, contractor turn over packs, etc.

- Tier 1: Record Data Book (RDB)
  The RDB should contain all records, latest revisions of drawings, and detail documentation for the project. Ideally, this should be broken out by discipline. In general, the RDB also should provide useful information for plant engineers, supervisors, maintenance personnel, as well as regulatory authorities.

- Tier 1: Commissioning and Qualification Documentation
  The commissioning and qualification documentation should be a collection of documentation packs generated by commissioning and qualification engineers to prove systems, plant, and equipment are acceptable for production and where applicable to regulative authorities.

- Tier 2: Construction Management Turnover Pack
  Construction Management TOP should be a collection of construction documentation generated by construction manager's sub-contractors and should include:
  - Electrical and Instrumentation Contractor's Turnover Packs
  - Mechanical Contractor's Turnover Packs
  - Civil Contractor's Turnover Packs

### 4. Establishment of Appropriate Field Procedures

The CQM manager should identify and establish appropriate field testing procedures necessary to execute the project. The field testing procedures may include procedures that govern protocol and documentation formats, testing and inspection procedures (as occasionally provided by sub-contractors as part of their quality program), documentation storage and distribution procedures, and project punch-list procedures.

### 5. Training of Key Personnel and Contractor Staff

The quality culture of "right first time" should be developed within the project team through a training program. All key construction personnel and sub-contractor staff directly involved in completing documentation for project turn-over packs should be trained, as a minimum, in Good Documentation Practices, as well as relevant SOPs

and field procedures established for the project.

### *6. Traceability and Control of Field Changes*

During the design/engineering phase, design changes are usually managed and controlled extremely well. However, the management and control of field changes is usually overlooked. Often there are more changes in the field then there are in the design phase. Therefore, traceability and control of field changes should be a high priority for the overall project team, as field changes may compromise operability, safety, quality, schedule, and costs.

The CQM manager should ensure, as a minimum, that field changes are properly assessed from a safety, quality, schedule, and costs perspective. He also should ensure that the field changes are recorded, properly documented, dated, assigned accountability, audited, signed, and properly filed. "Red flag" items should be prioritized for action.

### *7. Use of Appropriate Construction Forms*

All check forms to be used for system fabrication, installation, and testing should be in compliance with Good Engineering Practice requirements. The forms also should be checked for suitability and contents as they may be used as leveraged data, hence, eliminating duplication of effort.

## Case Study: Construction Quality Management (CQM)

### *Background*

In 2002, Eli Lilly committed to build a new biotech facility in the USA, which was critical to its long term strategy in biotechnology. The facility incorporated nearly 500,000 sq. ft. of laboratory, pilot plant, and administrative space and cost more than $200 million.

Several years prior to this project, Lilly had spent significant effort in strengthening its Commissioning and Qualification (C&Q) programs throughout the corporation. These improvements were based largely on the ISPE Baseline® Guide for Commissioning and Qualification, Volume 5. This effort had resulted in the development of a well defined and structured C&Q program, which helped deliver a better quality of deliverables, but most importantly, provided significant cost and schedule savings in the delivery of capital projects. As a result of this effort, Lilly's Corporate C&Q Group recognized that "construction quality" was critical to the success and efficiency of the overall C&Q effort. As a result, Lilly set up focus groups which begun working with contractors in order to identify critical factors that improved construction quality. These focus groups in conjunction with local contractors, identified critical steps that affected construction quality and began implementing them on various projects that were being executed by Lilly.

When Lilly issued the request for proposal for the new biotechnology facility, it included a requirement

*Continued on page 68.*

that bidders submit their Corporate Construction Quality Program and specifically their plan for managing quality on Lilly's new biotech project. The ability to clearly articulate a well defined construction quality program/approach for the project was a significant factor in awarding the contract.

### *Construction Quality Management (CQM)*

Following award of the contract, Lilly chose to appoint a third party CQM manager to help manage the overall construction quality for the project. The CQM manager worked in partnership with Lilly to set-up a CQM program to provide "quality" oversight, similar to programs used for contractor "safety" and worked closely with the Lilly C&Q team. At the outset of the project, both Lilly and the CQM manager recognized that this was a learning opportunity for understanding how to effectively manage construction quality and understand the benefits.

The CQM manager performed inspections, but did not take responsibility for quality away from the contractors. The CQM manager's activities included, but were not limited to the following:

- auditing the contractor's quality program to assure it was functioning
- holding meetings with sub-contractors to review job quality plans (required for sub-contractors)
- holding weekly quality meetings to review and follow-up on quality issues discovered on the project
- performed job site inspections across multiple phases of the project and tracked and reported metrics to Lilly and the contractor

As the project progressed, it became apparent that meeting the project completion date had become paramount for the business owner to meet critical business objectives.

### *Findings*

The CQM effort identified and managed a considerable number of construction related quality issues throughout the construction phase of the project. The types of findings varied significantly in potential impact on cost and schedule.

Some findings were relatively minor in potential impact on cost/schedule, while others had the potential to significantly delay the commissioning/qualification phase of the project. In one particular case, a quality issue had the potential to cause major catastrophe had it not been identified and resolved early in the project by the CQM team.

Findings were recorded in Quality Observation Reports (QORs) and entered in a database with a unique identifying number. (There are various off-the-shelf databases commercially available such as Latista, Vela Systems, etc.).

In many cases, a photograph also was taken and captured in the data base, together with the QOR. The photographic records proved to be extremely useful because these enabled field issues to be visually displayed to the sub-contractors, which in turn helped clarify the issue and avoid further discussions/debates. In addition, a date for resolution of each issue was assigned to each QOR. Weekly quality meetings also were held by the CQM group together with the sub-contractors, in order to discuss new findings and status of previous findings. These meetings were extremely valuable in maintaining focus on field issues and driving resolution. The proactive and systematic management of the field issues prevented the typical build up of issues at the end of the project.

Typical examples of field issues that were identified included:

- Steel Shear Tears
  Shear tears were noticed on the ends of multiple support angles being used in building erection - *Figure 6*. It was confirmed that the tears were preventing the welds from penetrating the steel. The welds were not bonding the steel in any way. As a result, all steel angles were repaired to provide efficient bonding surfaces before installation. Analysis was completed to prevent future occurrences. This was primarily a structural issue, which if undetected and unresolved

| | | Potential Impact | | | | |
|---|---|---|---|---|---|---|
| **Example Issues** | **Type** | **Catastrophic Failure** | **C&Q Delay** | **General Delay and Repair** | **Safety** | **No Impact** |
| Roof Drains Installation | Mechanical | | | X | | |
| Weld Quality | Mechanical | | X | X | | |
| Welding Log Documentation | Mechanical | | X | | | |
| Missing Instruments | Mechanical | | X | | | |
| Equipment/Instrument Installation | Mechanical | | X | X | | |
| Damage Instruments/Equipment | Mechanical | | X | X | | |
| Tagging and Labeling | Mechanical | | X | | | |
| Insulation/Caulking | HVAC/Mechanical | | X | X | | |
| Out of alignment structure steel | Structural | | | X | | |
| Stair Risers not to spec. | Structural | | | X | X | |
| Room Finishes | Structural | | X | X | | |
| Storage of Materials | Material Management | | X | X | | |
| Mold on Walls | Material Management | | X | X | X | |
| Cable Installation | Electrical | | X | X | | |

Table A. Additional types of issues identified during the construction phase by the CQM effort.

would have caused significant cost and schedule delays.

- Drywall Mud Application Temperature
  Specifications called for drywall mud to be applied between 13°C and 26°C. Actual application was occurring at 3.3°C. Mud was removed and reapplied at proper temperature - *Figure 6*.

- Leak Detection Level Switch
  A leak detection level switch was installed in the wrong nozzle of a sump - *Figure 6*. This issue would have been ultimately discovered; however, by detecting and resolving the problem early, it prevented the issue from surfacing in the commissioning/qualification phase and causing a potential schedule delay.

- Missing Pressure Indicator
  Typical of QOR issues was a missing instrument that the drawings had indicated, but had not been installed - *Figure 6*. The CQM group identified and quickly resolved the problem with sub-contractors and prevented the issue from surfacing in the commissioning/qualification phase and causing a potential schedule delay.

- Shaft Wall Construction
  Elevator, mechanical, and stair shafts were not being constructed per detail. The contractor had decided to construct them as they did on previous Lilly projects. The head design of these shaft walls were designed for specific load ratings unique to this project. After design review by the A&E, it was apparent that failure would have almost certainly occurred had the rework not been performed.

  All walls in place were repaired and the intended design was implemented on remaining walls. Miscommunication and incorrect assumptions can create confusion regarding specifications and expectations. This finding alone and its potential safety implications justified the entire CQM program on the project and reinforced the strong link between quality safety.

Additional types of issues identified during the construction phase by the CQM effort included the following:

### *Results*

The CQM manager and Lilly worked very closely throughout the project to manage quality with the construction manager and were able to have significant impact on the project. The premise of the effort was that improved construction quality would result in less construction related issues appearing during commissioning. As a result, the team responsible for executing the commissioning would be able to test and approve systems in a timely manner with fewer issues and deliver the facility to the customer on-time and at or below cost.

*Continued on page 70.*


Figure 6. Typical construction quality related issues.

As a result of applying the CQM Program, the following was observed:

- **14,921 Issues Identified**
  Each issue was catalogued in a database and tracked to closure by the CQM manager and the contractor. (See Figure 6 for typical construction quality related issues).

- **35.4% of Issues Identified were Potentially Commissioning Impacting**
  It was determined that 5,247 of the issues (35.4%) were determined to have potential impact on the ability to commission to facility.

- **2.0% Impacted Commissioning**
  A total of 303 items or 2.0% of all items were discovered in commissioning that could impact commissioning. Most of these items were minor and had minimal impact.

- **$2.8 Million Correction Pre-Commissioning**
  It was estimated that the cost of issues resolved prior to commissioning was conservatively around $3.0 million. These issues were identified by CQM manager and corrected/paid for by the contractor.

- **$380,000 Corrections during Commissioning**
  It was estimated that cost of issues resolved during commissioning was just under $400,000. These issues were identified by CQM manager and corrected/paid for by the contractor due to good tracking and issue resolution.

- **Contractors Retainage was Typically Paid Within 30 Days of Agreed Substantial Completion**
  Sub-contractors realized the management of quality throughout the project meant final closure and payment was more easily obtained.

The commissioning of the facility proceeded extremely well, coming in under budget, and meeting the timelines of the business owner. During the project, significant quality issues had been identified early and addressed in a timely manner. The contractor acknowledged to Eli Lilly management that without the CQM program it would have been impossible to deliver the project on-time and under budget.

### *Benefits*

Construction Quality Management needs to be a collaborative effort between the owner, designer, and construction teams. Clarity of expectations defined through accurate drawings and specifications is of paramount importance. However, good planning, communication, and proactive management of construction quality help establish a project execution focus and a "Right First Time" culture in the field.

The CQM approach outlined above was a minimal investment (i.e., 0.5% of Total Installed Cost, TIC) by the owner to assure field quality. The benefit achieved was a project delivered on time, under budget with quality issues addressed in a proactive, real-time manner, and paid for by the contractor; rather than have the issues surface during the commissioning/qualification phase or even later after transfer of custody to the owner.

Lilly has successfully used this approach with similar results on a manufacturing facility in Puerto Rico and has similar programs on-going with other capital projects in the United States, Ireland, and France.

### *Learnings*

In effectively implementing and managing the CQM program, the following important learning points were identified:

- **Real Time Management of Issues**
  It was important to identify and manage issues in a timely manner through regular meetings and this had the following impact:
  - reduced items at end of project
  - simplifies path to mechanical completion
  - allows to look for trends

- **Pre-Work Quality Meeting With Sub-Contractors Added Value**
  Meeting with the sub-contractors prior to beginning work, helped achieve the following:
  - verified that specifications were understood
  - assure training plans, inspection test plan, etc. were in place

- **CQM must be Managed**
  The CQM effort can be a cultural change and a challenge for contractors. It requires attention to detail, tracking of issues, and accountability. It requires focus and resources based on complexity of the project.

- **Field Inspection Reporting Program**
  A structured field inspection pro-

*Concludes on page 72.*

gram with scheduled and focused inspections by the inspection team and contractor is needed. This inspection program should include:
- engaged crafts people in identifying issues
- tracking program in place for issues

- **Metrics Provide Assessment Tool**
  Tracking metrics provide a mechanism for assessing program and providing timely feedback.

- **Effort must be Appropriately Scaled for Project**
  The level and degree of the CQM program can and must be scaled to the complexity of the project.

Finally, a member of the field execution team made the following statement,

***"Every time I walk on a job my eyes are wide open to "Safety" and now "Quality" as well. My experience on this project changed my mindset and awareness to the importance of construction quality."***

## Summary

Good construction quality is a prerequisite for successful commissioning and qualification. It is important to remember that "commissioning" is an iterative step that will help bring to life the ideas/concepts that were initially developed by the designers/engineers; and if executed properly, it can help successfully handover a facility from "field" to "operation and maintenance." "Qualification" on the other hand, is a step that will finally tell you what has "passed" and what has "failed," and one of its primary purposes is to facilitate regulatory compliance.

Typically, for $100 million (€100 million) Total Installed Cost (TIC) biotech facility, the commissioning and qualification costs (when utilizing a leveraged approach) would normally run anywhere between 2.5 to 5% of TIC, depending on complexity and level of sterility. However, in comparison, the construction quality management would typically run at around 0.5% to 1% of TIC. Therefore, a relatively small investment upfront in construction quality can bring huge benefits at the end of the project and beyond!

In reality, the true cost of failing to get your facility up and running on time is missing a launch date for a product or losing a race to market or not being able to maximize your revenue by not meeting market demand for a product.

## Conclusion

In conclusion, the selection of a good constructor is obviously very important; however, selecting a third party to perform CQM early on the project will have a very significant impact on the project outcome. A clear commissioning strategy, underpinned with a good CQM program, established at the preconstruction stage of the project, can help translate good engineering design into field execution/construction and help alleviate many of the problems encountered at the back end of a project. It also should give the overall project team a better chance of delivering the capital project on time, to budget, with good design, great quality, zero defects/accidents, good operability and maintainability, as well as high availability and reliability!

## About the Authors

**Jay Lad** is the Managing Director of SPGL (formerly the business of Skanska Pharmaceutical Group Ltd.), leading its construction quality, commissioning, qualification, and regulatory compliance services globally. He is a chartered chemical engineer with nearly 20 years of experience in the pharmaceutical and biotechnology industry, covering facility and process design, construction, commissioning, qualification, and project management. Lad has worked in a variety of sectors, including bulk, pharmaceutical, biotechnology, and medical devices and has considerable experience managing commissioning/qualification businesses in the pharmaceutical and biotechnology realm. He holds a BEng. in chemical engineering, graduating with honours, from the University of Bradford in the United Kingdom and he has previously worked for several EPC contractors, including Raytheon, AMEC, Washington Group International, and Skanska. He can be contacted by telephone: +44 (0) 7970-652-880, +44 (0) 20-7084-6873, or by email: jay.lad@spgl.eu.

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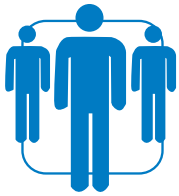

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**Jon Clark and Cliff Campbell discuss the findings of a project to determine a regulatory approach for a firm to change the manufacturing site for sterile drug products without requiring manufacturing data before approval.**

# PHARMACEUTICAL ENGINEERING Interviews

## Jon Clark, Associate Director for Policy, CDER Office of Pharmaceutical Science (OPS), FDA, and Cliff Campbell, CEO, Campbell Informatics

**Jon Clark** is an Associate Director for Policy, Center for Drug Evaluation and Research (CDER), US FDA. After 12 years of experience working in industry, Clark joined the Agency in 1992. He develops guidance documents, is a policy expert, contracts strategic research programs, and manages the environmental assessment review and the compendial operations. Clark is engaged in the Pharmaceutical Quality CGMPs for the 21st Century program, Critical Path Initiative, the Product Quality Research Institute (PQRI), and the International Conference on Harmonization (ICH). From 1980 to 1992, he was employed as an organic synthesis research chemist, first at Beecham Laboratories then at Schering Plough Research, producing various chemical processes, publications, and patents. Clark received his BS in chemistry at the University of Michigan in 1980 and his MS in chemistry at Rutgers University in 1987.

**Cliff Campbell** was educated at University College Cork, and is founder and CEO of Campbell Informatics, a company that provides knowledge management frameworks and consultancy to life-science manufacturers on an international basis. He has been an advocate of intrinsic quality and modular compliance for many years, promoting a back-to-basics approach to the itemization, characterization, and verification of systems and processes across their CMC, QbD and C&Q lifecycles. Campbell is a recognized driver of 21st Century Compliance and was appointed consultant to the FDA's Office of Pharmaceutical Science (OPS) in mid-2008, leading a 12-month assignment on Assessing Risks of Changing Sterile Drug Manufacturing Sites.

**Q** What was the assignment's official title?

**Clark:** Assessing Risks of Changing Sterile Drug Manufacturing Sites.

**Q** What was the underlying objective?

**Clark:** We wanted to explore different regulatory approaches for a firm to change manufacturing sites without requiring manufacturing data before approval.

**Campbell:** The assignment was targeted at sterile manufacturing, both synthetic and biotech, with the core objective as follows: to demonstrate that the risks associated with changing (i.e., relocating or expanding) the manufacturing site for sterile drug products (from formulation to fill) can be managed strictly within the manufacturer's change control process so that a supplement to an application is not required.

**Q** Can you provide some additional background from an Agency perspective?

**Clark:** Yes. It is seen as unnecessarily cumbersome to require manufacturing data in order to confirm criteria that are well established by other means.

*Continued on page 42.*

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# Pharmaceutical Processing Systems

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**Campbell:** From an OPS perspective, changing sterile drug product manufacturing sites is considered a major change, requiring applicants to submit a supplement to their applications. OPS has embraced QbD as a means of ensuring that risks associated with manufacturing changes – which still remain major – can be managed within the manufacturer's change control process and as part of current Good Manufacturing Practices (cGMPs). The authorization to do this would be granted through Agency approval of the applicant's Risk Management Plan.

**Q** What type of risks were you mainly concerned with?

**Clark:** Sources of variability and sources of impurity – and the risk of not meeting the requirement for sterility.

**Campbell:** Specifically, sterility assurance failures due to variations in facility, manufacturing process, design space, and/or process control strategies (e.g., validation, sampling, monitoring, and acceptance criteria), and the introduction of impurities to a drug product as a result of changes, raw materials, equipment, and/or container closure components.

**Q** Can you summarize deliverables, schedule etc?

**Campbell:** The assignment ran from July 2008 to June 2009 with the following deliverables:

| | |
|---|---|
| • Work Plan | 2 months |
| • Synthetic Drug: | |
| Interview Summaries | 3 months |
| Final Report | 2 months |
| • Biotech Drug: | |
| Interview Summaries | 3 months |
| Final Report | 2 months |

**Q** Can you tell us which companies participated in the interview process?

**Campbell:** Allergan, Amgen, Genentech, GSK, Genzyme, Pfizer, Solvay, Wyeth.

The National Institute for Pharmaceutical Technology and Education (NIPTE) in the US and University College Cork in Ireland also contributed from an educational perspective.

**Q** Was the assignment conducted as part of a Cooperative Research and Development Agreement (CRADA) or was some other format applied?

**Clark:** The assignment was performed as a research contract. The concept was published as a Request for Proposal (RFP) and was open to all bidders. The FDA will own the reports that are produced.

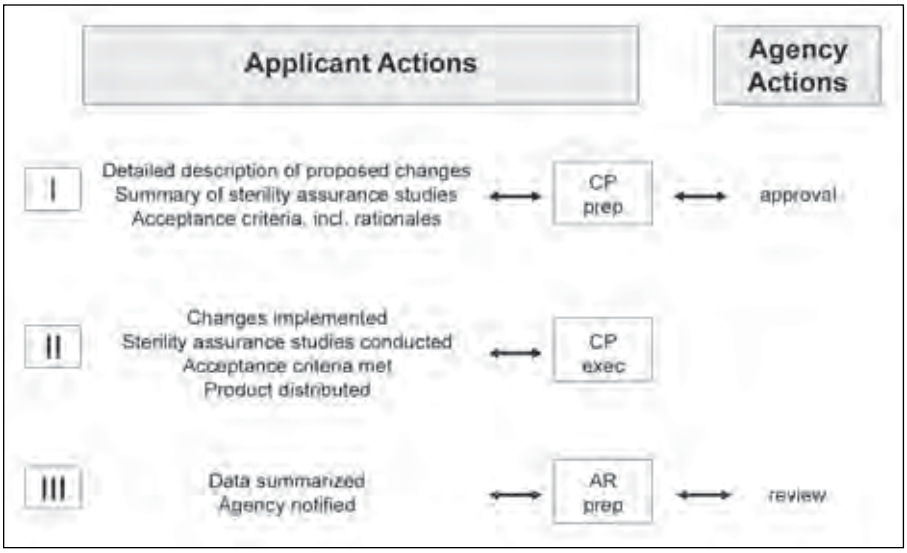


Figure 1. Summary of applicant and agency actions.

**Q** Can you describe the interview process and how the interviews were documented?

**Clark:** The FDA required that Office of Management and Budget (OMB) requirements for this kind of survey work be followed. We also allowed for the contributing parties to remain anonymous.

**Campbell:** Based on the assignment scope, the following topics were included within the interview process:

- Facility/Equipment
- Environment
- Raw Materials
- Process/Controls
- Components/Closures
- Personnel

In line with the agreed scope of work, synthetic product interviews focused on Terminal Sterilization (TS) and biotech products on Aseptic Processing (AP). Existing FDA guidance in regard to these two areas was examined relative to the above topics and selectively converted into abbreviated checklist form, separate checklists being compiled for TS and AP. Once approved by OPS, these were used to drive the interview sessions, these being conducted in workshop format at individual participant sites. The above process was not a survey, the intent being that the checklists would kick-start a general discussion in regard to the topic in question. In addition to the checklists, several participants provided additional material in support of their chosen approach. The interview sessions were individually documented, the write-ups being previewed by the relevant firm before being presented to OPS.

**Q** Can you describe the final reports and how these were documented?

**Clark:** These were documented as fictional case study submissions to the Agency with the purpose of changing manufacturing sites.

**Campbell:** The contract requirement

was that the reports be written as Risk Management Plans. In summary, the preferred Agency format was a Comparability Protocol, based on FDA's MAPP 5040.1 Policy (Product Quality Microbiology Information in the Common Technical Document – Quality). This would provide product quality microbiology reviewers with a familiar format, and one that could be mapped to an applicant's original application if required.

**Q** What were the major findings?

**Clark:** The main finding was that the use of a change protocol under 21 CFR 314.70(e) was a feasible approach. This makes implementation easier since some reviews have already been done this way.

**Campbell:** The first key finding is that, properly written, the Risk Management Plan and the Comparability Protocol are the same document, and that these in turn are identical to the traditional Prior Approval Supplement, minus the executed data, which is referenced in summary format in Annual Report. This is shown schematically in Figure 1.

The second finding again relates to comparability, and is a corollary to the above. In many interviews, what was presented in support of inter-site comparability was a gap analysis, which concentrated primarily on the physical or plant layer. What emerged in the course of the assignment is that if Site A and Site B are independently assessed relative to their 'mother spec' (MAPP 5040.1 etc.) then line-by-line comparisons between the two sites are no longer required, comparability becoming an inferred process.

**Q** Where does Failure Mode and Effects Analysis (FMEA) fit in to all of this, and what are the implications, if any, for risk-based C&Q?

**Clark:** FMEA is one of a number of techniques that could be used as a way to organize the information in a coherent way. For example, a firm could use the existing Common Technical Document format and embed FMEA approaches within a protocol this way.

**Campbell:** C&Q was addressed as a standard topic within the Facility and Equipment section of the interviews. From the point of view of current practice, most participants use ISPE's system and component impact assessment process to prioritize and manage their C&Q protocol preparation efforts, even though there is some variation in the extent to which leveraging is applied. A minority of firms are examining ASTM E2500 either as an alternative or as a complement to ISPE. The key issue from a qualification point of view is that, regardless of which qualification model is being used, the commit-

*Concludes on page 44.*


Figure 2. MAPP 5040.1.

ments contained within MAPP 5040.1, etc., are fundamental, and cannot be abbreviated or sidestepped based on risk-assessment.

**Q** Were there any significant differences in findings between Synthetic and Biotech?

**Clark:** Other than the differences between the two technologies, no regulatory differences are expected.

**Campbell:** The two sets of interviews were conducted independently, but commonality quickly became apparent, perceived differences between the product types soon disappearing. In both cases, there was general awareness by participants of the existence, rather than line–by-line content, of prevailing regulations. In many cases, the level of documentation that was presented in support of a particular task or work-practice was probably excessive. The best example of this was the absence of big-picture process flow diagrams capturing process steps, critical quality attributes, critical parameters, in-process controls, static and dynamic environmental monitoring, human interventions, and holding periods.

**Q** Was the topic of outsourcing and contract manufacturing addressed?

**Clark:** Yes. Other than the expected impact that contract manufacturing has on the existing framework, nothing new is expected with the advanced approach that we are proposing.

**Campbell:** Outsourcing was a cause of some concern to OPS, but participant response was consistent and unequivocal: outsourcing is non-contentious as long as it accompanied by the appropriate level of GMP audit and the necessary Quality Agreements are in place between the contract giver and contract receiver.

**Q** How does the assignment integrate with similar initiatives by other groups [e.g., Product Quality Lifecycle Implementation (PQLI), Product Quality Research Institute (PQRI), PDA, etc.]?

**Clark:** The question is too broad to answer. We have found no conflict with these other initiatives, but these deal primarily with specifics, whereas we were more interested in framework.

**Q** How will the assignment's findings be documented and disseminated?

**Clark:** Public workshops and publications will be used to disseminate the information.

**Campbell:** The information will be disseminated by interviews such as this, by white paper(s), and presentations at society annual meetings, etc. Note that the specific interview summaries are not being circulated, due primarilyto the issue of confidentiality. However, the real benefit of the assignment is not so much in the fine detail, but in the general findings relating to criticality and comparability.

**Q** Are FDA's other divisions (OC, ORA, ONDQA) on board or is this a standalone OPS initiative?

**Clark:** This initiative was championed by OPS and involved the review microbiologists for new drugs.

**Q** Was the assignment actual or hypothetical, and what level of regulatory flexibility is available to industry in the here and now?

**Clark:** The assignment was hypothetical, but the regulatory approach that was described is available immediately since it does not conflict with existing regulation or recommendations.

**Q** Will the findings become the basis of an Agency guidance or policy?

**Clark:** It is possible to be expressed as a guidance document for industry or become policy. However, the existing regulation is adequate for this use.

**Q** Is the Agency considering expanding this initiative to include API processes?

**Clark:** It is possible to expand this concept into other areas, but the initiative needs to come from within those groups.

**Q** A final question... what's in it for industry?

**Clark:** The potential to provide a basis for site change criteria that are traceable to the patient and do not require manufacturing data before approval.

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**This article presents a universal method to select and test weighing instruments based on an integrated qualification approach. Considering primarily the user's weighing requirements and risks, it describes a state-of-the-art strategy to ensure reliable weighing processes embedded in any current quality management system.**

# Good Weighing Practices for the Pharmaceutical Industry – Risk-Based Qualification and Life Cycle Management of Weighing Systems

by Arthur Reichmuth and Dr. Klaus Fritsch

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## Introduction

Weighing is only the first step of a whole analysis chain in drug discovery and quality control. The quality of weighing strongly influences the quality of the end result so that the US Pharmacopeia specifically requires highly accurate weighing results for assay.[1,2] Good Weighing Practices[3] provide a scientific methodology to selecting and testing weighing instruments within an integrated qualification approach. Based primarily on the user's weighing requirements and prevailing weighing risks, they provide a state-of-the-art strategy to reduce measurement errors and to ensure reliable weighing results. The understanding of weighing process requirements and important balance properties as minimum weight is essential to select an appropriate weighing system in the framework of the design qualification. The performance qualification takes into account these requirements and risks to establish a specific routine testing scenario for the instrument. The higher the risk in case of malfunctioning, and the more stringent the weighing accuracy requirements are, the more frequent balance tests have to be carried out. However, for less risky and stringent applications, testing efforts can be reduced accordingly. Risk- and life cycle management form an integrated part of the overall strategy of Good Weighing Practices to bridge the gap between regulatory compliance, process quality, and cost consciousness.

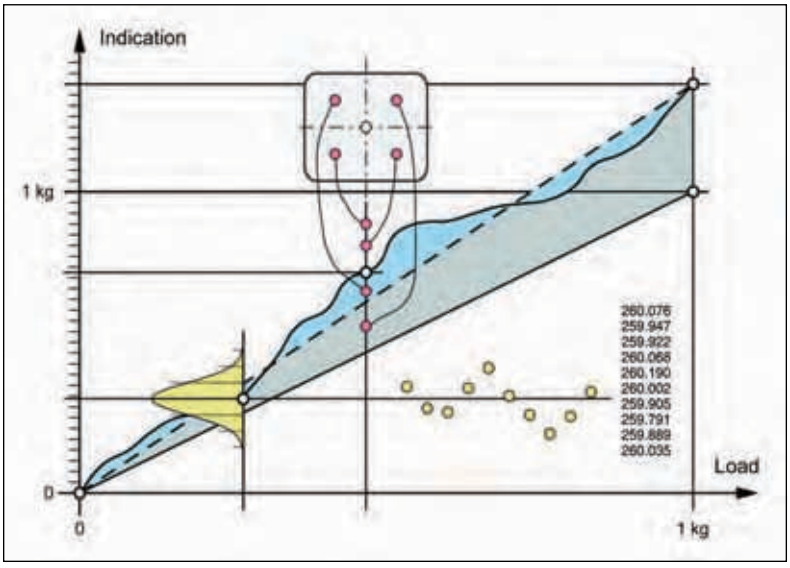


Figure 1. Balance properties: the dashed line with the associated gray area represents the sensitivity offset of the balance, superimposed is the nonlinearity (blue area, indicating the deviation of the characteristic curve from the straight line). The red circles represent the measurement values caused by eccentric loading, and the yellow circles represent the distribution of the measurement values, due to repeatability.

## Selecting a Weighing Instrument

### *Specifications and Uncertainty*

"I want to buy an analytical balance with a readability of 0.1 mg, because that is the accuracy I need for my application."

Statements like this are often heard when establishing a design qualification. In the wake of this requirement, a user may select an analytical balance with a capacity of 200 g and a readability of 0.1 mg, because it is believed that this balance is "accurate to 0.1 mg." This is a misconception for the simple reason that the readability of an instrument is not equivalent to its weighing accuracy.

*Continued on page 48.*

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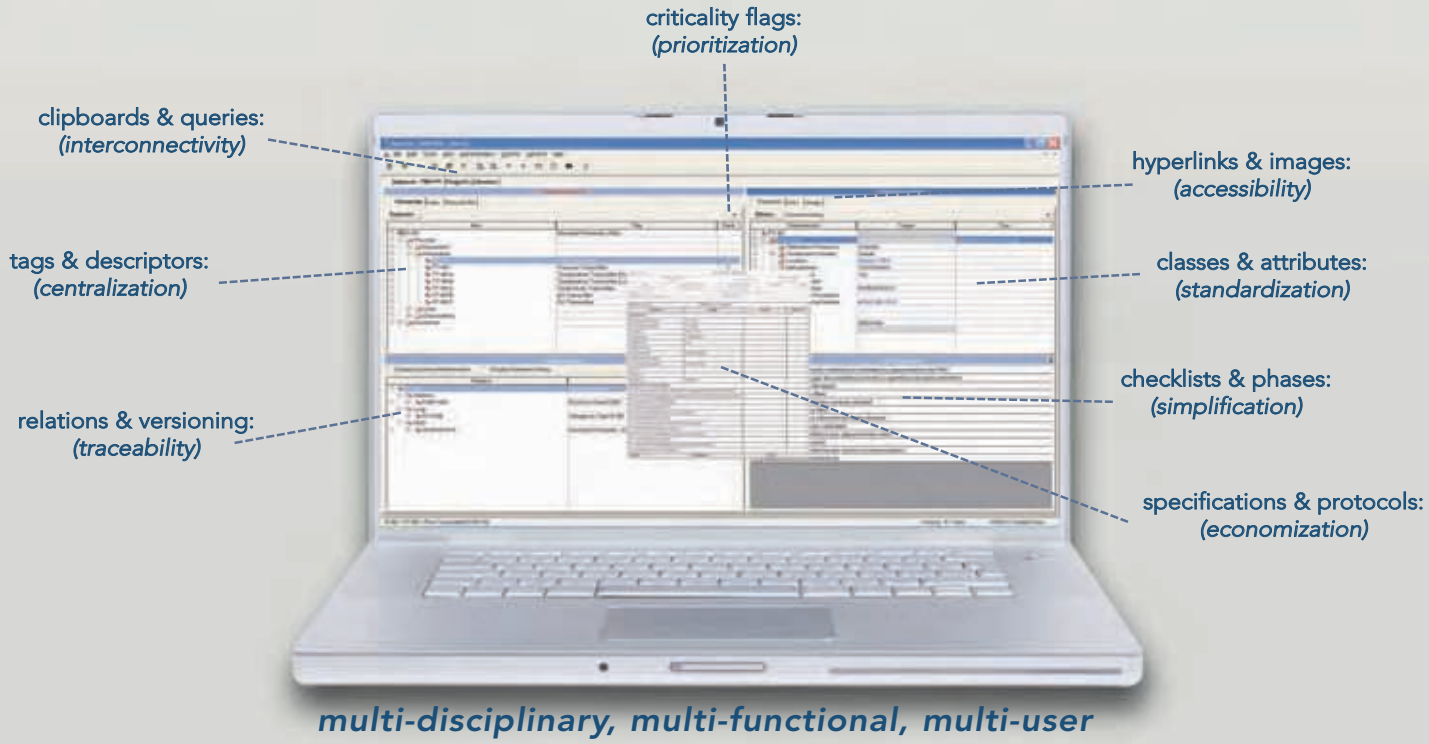


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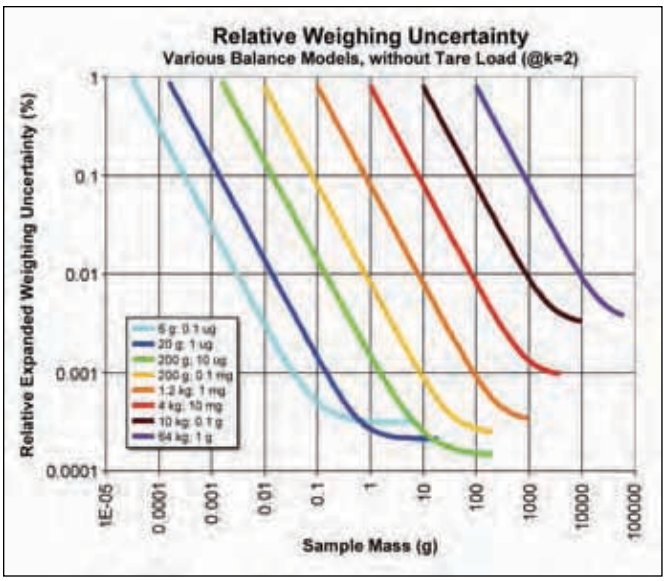


Figure 2. Relative weighing uncertainties of various balances, from an ultra-microbalance with a readability of 0.1ug to a precision balance with 1g. Shown is the relative uncertainty U (in %) versus sample mass m (in g). Uncertainties are estimated from typical specifications of the balances, and are expanded with a factor k = 2, with the assumption of zero tare load (i.e., gross load = sample mass).

There are several properties, quantified in the specifications of the weighing instrument, which limit its performance. The most important are repeatability (RP), eccentricity (EC), nonlinearity (NL), and sensitivity (SE), which are graphically displayed in Figure 1, and in detail explained in the respective technical literature.[4] How do they influence the performance, and hence, the selection of a weighing instrument?

To answer this question, the term "weighing uncertainty" must first be discussed. The "International Vocabulary of Metrology"[5] defines uncertainty as a parameter which expresses the dispersion of the values of a measurement.

The weighing uncertainty, i.e., the uncertainty when an object is weighed, can be estimated from the specifications of a balance (typically, the case when performing a design qualification) or from test measurements with the weighing instrument (typically the case when carrying out an operational qualification or performance qualification) or from a combination of both. The essential influences can be combined according to statistical methods to obtain the weighing uncertainty.[6]

Uncertainty can be expressed either as standard uncertainty $u$ (corresponding to the standard deviation of a statistical process) or as expanded uncertainty $U$, also referred to as "uncertainty interval." To obtain the expanded uncertainty, the standard uncertainty must be multiplied with the expansion factor $k$. Figure 2 shows uncertainties of various balances, which were estimated according to these rules from their typical specifications.

What can be deduced from Figure 2 is that the uncertainties as a function of the sample mass behave similarly for all balance models. It is their "position," i.e., their location relative to the axes of sample mass and uncertainty, which is dependent on the model of balance. The characteristics of this behavior become more obvious from Figure 3, where the individual contributing components are shown. The uncertainty as a function of the sample mass can be separated into three distinctive regions:

1. Region 1 with sample masses less than the lower rollover limit mass (i.e., largest sample mass, at which the contribution of repeatability dominates uncertainty). It is about 10 g in this specific example, and indicated yellowish in Figure 3. As repeatability is a weak function of gross load (if at all), the relative uncertainty decreases inversely proportional to the sample mass.
2. Region 2 with sample masses larger than the upper rollover limit mass (i.e., smallest sample mass, at which the contributions of sensitivity offset and eccentricity dominate uncertainty. It is about 100 g in this specific example, and indicated as greenish in Figure 3). The relative uncertainties of these properties are independent of sample load; consequently, the combined relative uncertainty remains (essentially) constant.
3. Region 3 is the transition region with sample masses between the lower and upper rollover limit mass, where the uncertainty rolls off from inverse proportionality to a constant value.

Moreover, for a majority of laboratory balances, nonlinearity hardly contributes a significant part to uncertainty, as its relative uncertainty, over the entire range of sample mass, is smaller than any other contribution.

### *Essentials to Select a Weighing Instrument*

With these facts in mind combined with the knowledge of the weighing accuracy required for an application and the mass

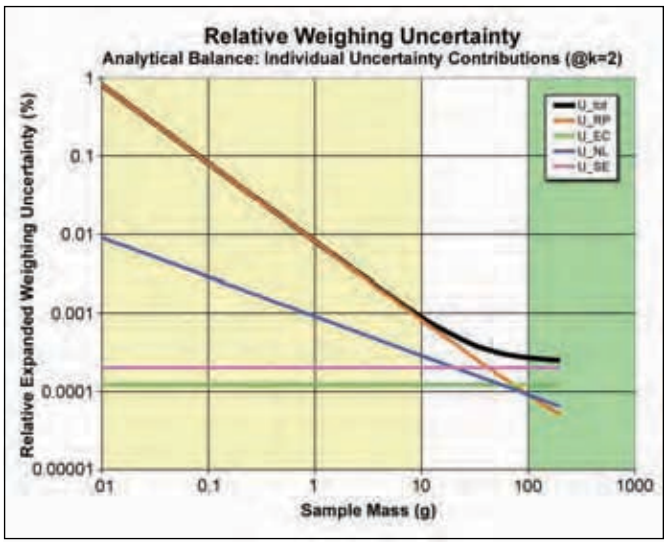


Figure 3. Relative weighing uncertainty versus sample mass (with zero tare load) of an analytical balance with a capacity of 200g and a readability of 0.1g (U_tot, thick black curve). The contributing components to uncertainty also are shown: repeatability (U_RP, orange), eccentricity (U_EC, green), nonlinearity (U_NL, blue) and sensitivity offset (U_SE, pink). Uncertainties are expanded with a factor of k = 2. Repeatability dominates uncertainty in the yellowish region, sensitivity or eccentricity in the greenish region.

*Continued on page 50.*

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of the sample to be weighed, two essential selection criteria for a weighing instrument can be formulated:

1. The capacity of the weighing instrument must be larger than or equal to the largest gross load, i.e., the sum of the tare load and the sample (or net) load to be handled in the application.
2. The uncertainty when weighing the smallest sample must be smaller than or equal to the accuracy required ($A_{req}$) by the user's application.

If a weighing instrument meets these two conditions, it is in principle suitable for the application. The second condition is also known as "minimum weight condition." For a small sample mass, repeatability is the dominating contribution (yellowish region, Figure 3) from which the smallest mass, satisfying the required accuracy, can be calculated. This amount of mass is referred to as "minimum sample weight," or simply "minimum weight." If the minimum weight of a balance is unknown, it can be determined from repeatability. Because a small sample weight lies in region 1, repeatability ($s_{RP}$) is the only balance property on which the minimum weight depends.

$$m_{min} = (k/A_{req}) \cdot s_{RP}$$

As discussed above, it is not the readability that determines the accuracy of a weighing instrument, but rather its repeatability, or depending on it, its minimum weight capability. Note that the determination of the minimum weight from repeatability also is a consequence of the requirement of USP General Chapter <41> "Weights and Balances," which states: "Unless otherwise specified, when substances are to be "accurately weighed" for *Assay*, the weighing is to be performed with a weighing device whose measurement uncertainty (random plus systematic error) does not exceed 0.1% of the reading. Measurement uncertainty is satisfactory if three times the standard deviation of not less than 10 replicate weighings divided by the amount weighed, does not exceed 0.001."[1]

### *Example*

A company needs a balance for their QC department. At a specific point in the weighing process, the mass of samples as small as 20 mg must be determined with a relative weighing accuracy of 0.1%. The gross load is limited to 50 g. What balance suits this application?

From these givens, it can be concluded that any balance with a capacity of 50 g or more (rule 1), and a minimum weight capability of 20 mg or smaller (rule 2) is a candidate for this application. Most likely a semi micro balance (with a readability of 10 ug) would be chosen. If the minimum weight of the balance would not be known, the equivalent repeatability can be calculated instead. With an expansion factor of k=3, and the required accuracy of 0.1%, the equivalent required repeatability is:

$$s_{RP} = (A_{req}/k) \cdot m_{min} = (0.1\%/3) \cdot 20\ mg = 0.007\ mg$$

In other words, a balance with a repeatability of smaller than 0.007 mg has to be chosen to fulfill the user's weighing accuracy requirements.

### *Safety Factor*

Repeatabilities determined from a limited number of on site weighings will vary, even if the setup is left unaltered. Note that the standard deviation of a random variable is itself a random variable. For example, the standard deviation calculated from the readings of 10 weighings of the same object may accidentally exceed the true value of repeatability by as much as 180% or underestimate the true value by as low as 70% on a 95% confidence level.

Besides these statistical variations, environmental conditions, labware used, or the operator may change, influencing the performance of the weighing instrument. Therefore, it is recommended to apply a safety factor (not to be confounded with the expansion factor $k$), which establishes a safety margin between the accuracy limit of the instrument and the required weighing accuracy. It might be advisable to use a safety factor of 2 to compensate for the variation in the determination of repeatability. Note that only the calibration, i.e., the determination of the measurement uncertainty and the minimum weight of the balance at the final installation location, certifies the applicability of the balance for the specific weighing process. The calibration is done by an authorized service technician as part of an integrated qualification approach for the weighing instrument, and is periodically repeated thereafter.

Revisiting our example and applying a safety factor of 2, both the required minimum weight and the repeatability decrease by this factor. The required repeatability thus amounts to 3.5 ug, a value that a semi micro balance may not be able to provide. As an alternative, a micro balance (with a readability of 1 ug) could be used instead.

## Routine Testing of Weighing Instruments

*"Measuring equipment shall be calibrated or verified at specified intervals… against measurement standards traceable to international or national measurement standards."* ISO9001:2000, 7.6 Control of Monitoring and Measuring Devices

*"Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. It is the responsibility of the test facility management to ensure that instruments are adequate and functioning according to their intended use."* OECD Principles of GLP, 4.2 Use, Calibration, and Maintenance of Equipment

The statements cited above delegate the responsibility for the correct operation of equipment to the user. This also applies for weighing instruments. Statements like these are usually formulated vaguely, as they are meant as general guidelines. Therefore, they cannot be put to work for daily routine. Questions like, "How often should I test my balance?" emerge in situations where guidance is needed to design standard operating procedures that neither are too exhaustive, and thus

*Continued on page 52.*

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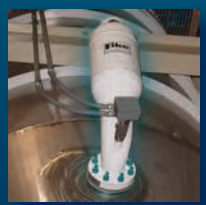

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are costly and time consuming, nor are too loose to assure the proper functioning of a weighing instrument. In order to realize an effective performance qualification as part of a life cycle management approach, the balance properties will have to be looked at a bit closer.

### Routine Test Procedures

Most likely, the majority of all samples being weighed on laboratory weighing instruments, especially in laboratory applications, satisfy the condition of being "small samples," i.e., samples with a net mass considerably smaller than the capacity of the weighing instrument, a few percent of capacity, say. When discussing the relative uncertainty versus sample mass, it was already mentioned that weighing uncertainty is governed by repeatability if a small sample is weighed - *Figure 3*.

Consequently, with the majority of weighing processes, repeatability is the most important contribution to uncertainty. This would be a good reason to test repeatability most frequently. However, this test comprises repeated weighings of the same test weight multiple times, usually around 10 times. To perform these tests properly, considerable effort and elaborated skills are required. On the other hand, the test of sensitivity can be carried out with one single weighing of a test weight, certainly less of an effort. What is more, the sensitivity test would reveal any serious problem with the instrument or if the result were to drift; in short, it may be regarded as an elementary test of the functionality of the weighing instrument. Although sensitivity is not the most critical property of a weighing instrument by far, the sensitivity test is proposed to be carried out with the highest frequency for the reasons cited, followed by repeatability with a lower frequency.

Revisiting Figure 3 and its explanations, it was said that eccentricity influences only weighings of samples with a considerable mass compared to the capacity of the weighing instrument, larger than a few percent, say. Besides, placing containers and samples in the center of the weighing platform or at least in the same place for the tare and the gross readings, the influence of eccentricity can be avoided entirely. This is the reason why eccentricity could be tested less frequently than repeatability or sensitivity. For less demanding applications it can even be dropped, as eccentricity also is assessed when the weighing instrument is calibrated by authorized personnel. For the least demanding applications, even the test of repeatability can be dropped.

Nonlinearity is not recommended to being tested by the user at all, as its influence on weighing uncertainty is inferior and hardly dominant with any model of laboratory weighing instruments; besides, it is being taken care of when the weighing instrument is calibrated by authorized personnel.

The following test procedures for weighing instruments are recommended in the framework of the performance qualification:

1. Calibration by authorized personnel, including the determination of weighing uncertainty or minimum weight, if applicable; the aim is to assess the complete performance of the instrument by testing all relevant weighing parameters of the instrument. Calibration also is an important step within operational qualification after the balance is installed and the necessary functional tests performed.
2. Routine test of sensitivity, repeatability, and eccentricity (but not nonlinearity), to be carried out by the user within defined intervals; the aim is to confirm its suitability for the application.
3. Automatic tests or adjustments, such as those of the sensitivity, carried out automatically by the weighing instrument; the aim is to reduce the effort of manual testing.

### Test Frequencies

The testing procedures and corresponding frequencies are based on:

1. the required weighing accuracy of the application
2. the impact (e.g., for business, consumer, or environment), in case that the weighing instrument should not function properly
3. the detectability of a malfunction

It is assumed that the more stringent the accuracy requirements of a weighing are, the higher the probability becomes that the weighing result does not meet the accuracy requirements. In this case, the test frequency is increased. Similarly, if the severity of the impact increases, the tests should be performed more frequently. That way, a higher impact is offset by more frequent tests, thereby lowering the likelihood of occurrence of the impact, and hence, offsetting the increase of risk that otherwise would occur - *Figure 4*.

If the malfunction of the weighing instrument is easily detectable, the test frequency is decreased.

The frequencies for the test of all properties extend from daily for risky applications (user or automatic tests), over weekly, monthly, quarterly, twice a year to yearly (e.g., calibration by authorized personnel).

### Test Limits – Control and Warning Limit

Routine tests are based on the required weighing accuracy for

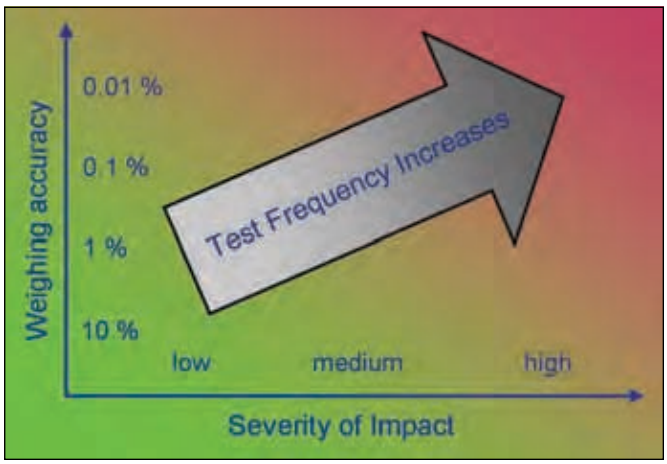


Figure 4. Test frequencies increase as a function of more stringent weighing accuracy and increasing severity of impact in case of an incorrect weighing (qualitative chart).

*Continued on page 54.*


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for an application. Simply speaking, the weighing accuracy must be better than or equal to the accuracy required. The required accuracy is referred to as Control Limit (*CL*), meaning that if this limit is exceeded, immediate action must be taken. It is recommended to introduce a Warning Limit (*WL*), the value of which is smaller than the control limit by a suitable factor, namely the Safety Factor (*SF*) introduced previously. The warning limit is obtained by dividing the control limit by the safety factor $WL = CL / SF$. This allows testing for the warning limit. If the warning limit is violated, there is still a safety margin before a process must be halted. This gives "room" for corrective actions.

Therefore, test results of each individual property are to be compared to warning limits, which in turn depend on the control limits via the safety factor. However, these deviations (sensitivity, repeatability, eccentricity, and nonlinearity) may occur simultaneously; thus, the sum of their deviations may be larger than the warning limit. A simple way to deal with this is to allocate only a part of the warning limit allowance to each individual property. This is achieved by dividing the warning limit by the Uncertainty Combination (*UC*) factor to obtain the test limit against which the individual test results are compared, accounting for the accumulation. For sample masses of a few percent of the capacity of the balance or higher, where repeatability is not dominant, the warning limit allowance is divided by the uncertainty combination factor of $\sqrt{(1+1+1)} \approx 1.73$, taking into account sensitivity offset, nonlinearity, and eccentricity, rounded up (for the sake of simplicity) to 2, yielding the warning limit applicable to each individual property. The warning limits for all properties (with the exception of repeatability) are obtained as follows:

$WL = m_T \cdot A_{req}/(SF \cdot UC) = ½(m_T \cdot A_{req}/SF)$ (limit value for sensitivity offset, nonlinearity, and eccentricity)

where $A_{req}$ is the required relative accuracy, *SF* the safety factor, $m_T$ the mass of the test weight.

Repeatability dominates uncertainty in region 1 (Figure 3, yellowish). In a laboratory environment, by far the most number of weighings of sample masses will occur in this region. Because in this region, the contributions of sensitivity offset, eccentricity, and nonlinearity to the overall weighing uncertainty are negligible compared the repeatability contribution, the allowance of repeatability needs not be reduced; thus, can be directly compared to the warning limit. Moreover, the standard deviation of repeatability is already expanded by $k$, the coverage or expansion factor.

For repeatability, the warning limit is expressed as standard deviation:

$WL = m_{S,min} \cdot A_{req}/(SF \cdot k)$ (limit standard deviation for repeatability)

where $m_{S,min}$ the mass of the smallest sample to be weighed and $k$ the expansion factor.

Figure 5. Two test weights are recommended. The large weight has a mass close to the nominal capacity of the weighing instrument, while the small weight amounts to a few percent of the nominal capacity. The large weight is used to test sensitivity and eccentricity, the small for repeatability (if required, together with an additional tare mass).

### Test Weights

"Which weight should I use to test my balance?"

For the user tests, two test weights are recommended - *Figure 5*.

1. A large weight preferably of a mass equal to the capacity of the weighing instrument. It is recommended to use the next available single weight denomination according to the OIML or ASTM classification, which is smaller than or equal to the nominal capacity of the weighing instrument.

2. A small weight preferably of a mass equal to a few percent of the capacity of the weighing instrument. It is recommended to use the next available single weight denomination according to the OIML or ASTM classification, which is smaller than or equal to 5% of the nominal capacity of the weighing instrument.

As further guidelines, the following rules are implemented:

1. Weights for the test of the sensitivity of weighing instruments need to be calibrated and must be traceable (reference weights). Their maximum permissible error (mpe) must not be larger than 1/3 of the warning limit so that its influence compared to the warning limit may be neglected. With this condition, the contribution of variance of the test weight is limited to less than 10% of the variance of the warning limit. The lowest weight class which fulfills this condition is selected. Since the warning limit depends on the control limit, and thus on the required weighing accuracy, so does the mpe of the test weight.

2. All other tests (i.e., tests of repeatability or eccentricity) may be performed with any weight, provided it does not change its mass during the test. Of course, it is always possible to use a calibrated test weight for these tests as well, but this is not required.

3. According to Figure 3, testing for sensitivity with a test weight which is too small (compared to the capacity

of the weighing instrument) runs the risk of the test measurement becoming "contaminated" by the influence of repeatability.

Test weights for sensitivity are typically of higher accuracy class (OIML F or E). However, even in cases where an OIML class M weight would suffice for a test, OIML class F2 weights should be used instead. The reason is that the surface of class M weights is allowed to remain rough.[7] This increases the chances for potential contamination, a feature which is not tolerated in laboratories. The same applies for ASTM weights where weight classes lower than ASTM4 should not be used in a laboratory environment.[8]

Test weights for sensitivity must be (re-)calibrated themselves in regular intervals to provide traceability.

### User Routine Tests

The following tests are recommended:

1. Sensitivity preferably with the large weight. At the user's discretion, the test can be performed with the small weight or at an arbitrary "operating point." However, there is a potential loss of test selectivity when using a small weight, i.e., the sensitivity test becomes contaminated by repeatability deviations - *Figure 3, region 1*. This may especially apply to test weights smaller than the second weight recommended.

2. Repeatability preferably with the small weight. It is recommendable to involve in the repeatability measurement tare weights or containers that will be used later. Tare weights, or even more so, vessels may degrade repeatability.[9]

3. Eccentricity preferably with the large weight.

Reassessing the example of weighing 20 mg with an accuracy of 0.1% (expansion factor $k$=3) on a micro balance with a capacity of 50 g, thereby applying a safety factor of 2, we are now able to determine the control and warning limits for the tests to be carried out with the two weights that are considered - *Table A*.

### How to Assess Repeatability?

As pointed out above, the majority of weighing processes take place with small samples. This is the case in a laboratory when weighing small amounts of substance in a vessel, for example. Therefore, it is reasonable to test the repeatability with a test weight in the order of a few percent of the capacity of the weighing instrument, rounded to the next weight denomination. While repeatability generally tends to increase with increasing gross load, this increase is usually feeble, a factor of 2 from zero load to nominal capacity, for example. Nevertheless, repeatability may be regarded as essentially constant for small sample weights, i.e., weighing processes

*Continued on page 56.*

| Balance capacity 50 g | | | Sensitivity | | Repeatability | | Eccentricity | |
|---|---|---|---|---|---|---|---|---|
| Smallest net weight 20 mg | | | CL | WL | CL | WL | CL | WL |
| Required accuracy 0.1% | | | | | | | | |
| Expansion factor k = 3 | | | | | | | | |
| Safety factor SF = 2 | | | $½(m_T \cdot A_{req})$ | $½(m_T \cdot A_{req}/SF)$ | $m_{S,min} \cdot A_{req}/k$ | $m_{S,min} \cdot A_{req}/(SF \cdot k)$ | $½(m_T \cdot A_{req})$ | $½(m_T \cdot A_{req}/SF)$ |
| Weight 1 | ≤ 100% of capacity | 50 g | 25 mg | 12.5 mg | --- | --- | 25 mg | 12.5 mg |
| Weight 2 | ≤ 5% of capacity | 2 g | --- | --- | 6.7 ug | 3.3 ug | --- | --- |

Table A. Example for calculating control and warning limits for user routine tests (sensitivity, repeatability, and eccentricity).

where the tare and gross loads are close to each other and therefore both readings exhibit essentially the same repeatability. This fact is depicted in Figure 6. It can be seen that the (absolute) uncertainty, and therefore the repeatability, as all other contributions are negligible, remains essentially constant for small sample weights (compared to the capacity of the balances).

If repeatability is a critical issue, it is recommendable to put the tare object (container, vessel, flask, etc.) on the weighing platform and to test repeatability with the test weight at this "working point." It should be mentioned here that not only the mass of a tare load, but also its dimensions may influence the repeatability of the weighing. On a semi micro balance, for example, repeatability might increase about five times when weighing a sample into a volumetric flask of 250 ml, compared to weighing the sample together with a compact tare of the same mass as the flask (around 90 g).[9]

### *Why can the Minimum Weight be Determined with a Test Weight Larger than the Minimum Weight?*

By definition, minimum weight is the lowest amount of sample mass that can be weighed, complying with a given required weighing accuracy. The most obvious method to test for minimum weight is to use a test weight with a mass of the (expected) minimum weight and determine the repeatability of the weighing instrument with this test weight. If the resulting weighing uncertainty is smaller than the required accuracy, the test passes, if it is greater, the test fails.

This method has several disadvantages:

First, if the test passes, there is no guarantee that there might not be still a smaller mass satisfying the accuracy requirements. To find out about this, the test needs to be repeated with a smaller test weight.

Second, if the test fails, the test needs to be repeated, too, but this time with a larger test weight. In both cases, the test may require an iterative approach, demanding more effort than just for one test. This is a waste of resources.

Third, using OIML test weights, as is very convenient, come only in denominations of 1-2-5 (for ASTM weights, the dominations are 1-2-3-5, accordingly). This means that a minimum weight of 45 mg, for example, could not be confirmed, unless the test is carried out with a weight combination of three weight pieces, namely 20 mg, 20 mg, and 5 mg. Needless to say that determining the repeatability with a test load composed of three test weights is a tedious and error prone task.

Fourth, minimum weight of analytical and microbalances are in the order of a few milligrams. Handling such a small weight is difficult, and the faintest draft may blow the weight away.

There is a more efficient method to test minimum weight. It bases on the fact that with all balances, repeatability is no function of sample mass, i.e., remains constant, as long as the sample mass is smaller than a few percent of the weighing capacity. With this knowledge, it becomes clear that the repeatability need not be determined with a test weight of the very minimum mass, but can be chosen larger, as long as the condition stated is met. The repeatability obtained from this test can then be used to calculate the minimum weight.

$$m_{min} = (k/A_{req}) \cdot s_{RP}$$

The advantages of this method are manifold:

- Only one test must be performed.
- The mass of the test weight can be chosen so that the test can be conveniently carried out.
- Intermediate, i.e., non 1-2-5 (1-2-3-5) values for the minimum weight are possible.

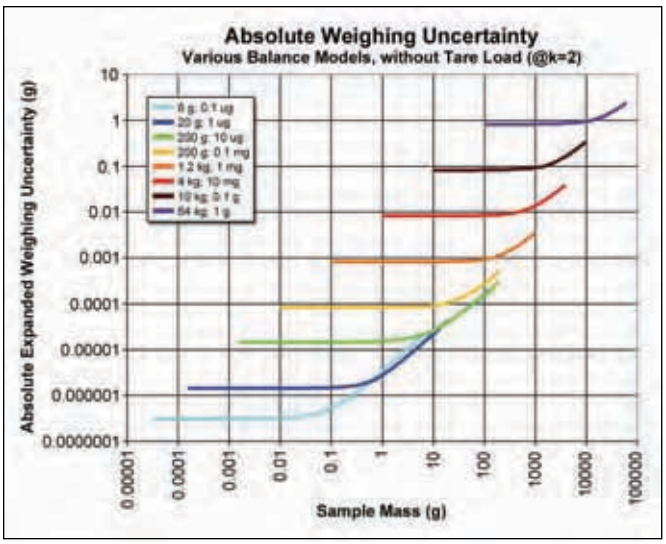


Figure 6. Weighing uncertainties of various balances, from an ultra-microbalance with a readability of 0.1ug to a precision balance with 1g. Shown is the (absolute) uncertainty U (in g) versus sample mass m (in g). Uncertainties are estimated from typical specifications of the balances, and are expanded with a factor k = 2, with the assumption of zero tare load (i.e., gross load = sample mass).

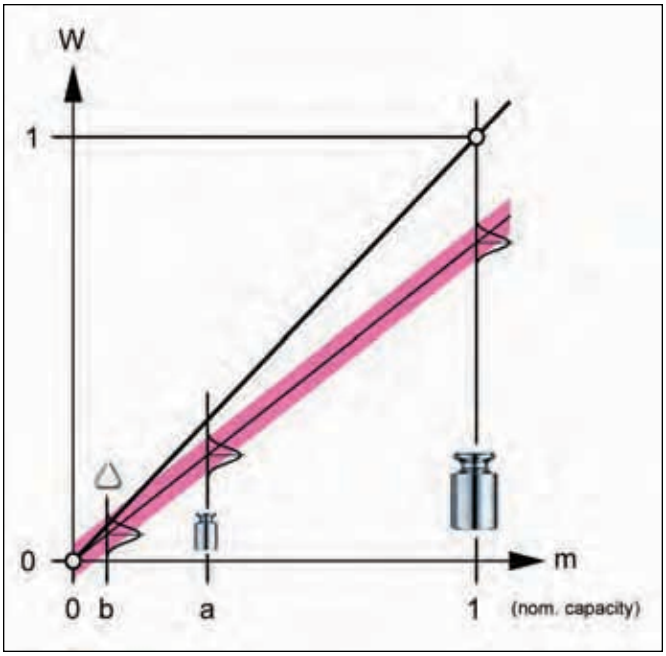


Figure 7. Sensitivity of a weighing instrument: shown is the displayed weighing value W versus the load m on the platform. To test for sensitivity, it is recommended to use a test weight close to nominal capacity.1 Using a smaller test weight (a < 1) results in a smaller measurable sensitivity offset, which is partially disturbed by repeatability (red band). Using a very small test weight (b < < 1) results in a measurable sensitivity offset which is buried entirely in the dispersion band of repeatability. (Remark: This diagram, and particularly the test masses of (a) and (b) weights, are not shown to scale.)

This fact also is considered in the latest draft revision of USP General Chapter <1251> "Weighing on an Analytical Balance" - *Table A "Suggested Performance Qualification Tests."*[10]

### *Why should a Test Weight Close to Capacity be Chosen for the Test of Sensitivity?*

Referring to Figure 3, region 1, where the sample mass is smaller than the lower rollover limit mass, 10 g in this example, it was said that repeatability dominates the uncertainty, i.e., all other properties (sensitivity, eccentricity, and nonlinearity) contribute negligible amounts to uncertainty, compared to repeatability. A test result in this region is contaminated by deviations caused by repeatability, the more so, the smaller the test weight becomes. Simply speaking, sensitivity is buried in repeatability - *Figure 7*. Therefore, a test weight close to capacity should be chosen.

### *Instruments with Automatic Test and Adjustment Features*

"What is the importance of the adjustment with built-in weights versus a test with an external weight?"

Adjustment mechanisms built into weighing instruments consist of one or more reference weights, and a loading mechanism that is actuated either manually or automatically. Such a mechanism makes it possible to conveniently test or adjust the sensitivity of the weighing instrument. Because the built-in weight cannot be lost, cannot be touched, and is kept in a sheltered place inside the instrument, this concept has advantages over testing or adjusting with an external weight, which is vulnerable to damage, dirt, and other adverse effects; besides, it allows to substantially reduce the frequency of such tests or adjustments with external reference weights.

However, because the built-in test weight is not accessible, it cannot be declared as being traceable since traceability requires that the weight can be removed and compared periodically with another reference of a higher class, which is not possible. Nevertheless, the built-in weight can be tested against an external reference by comparing the weighing result of the built-in weight with the weighing result of an external reference weight, which is weighed immediately thereafter, the very weighing instrument being the comparator. With this comparison, the integrity of the built-in calibration mechanism can be tested.

If a weighing instrument features such an adjustment mechanism, it should be (frequently) used, as it is a procedure that requires little to no effort with the exception of a short interruption of use to the instrument. As a consequence, routine tests of sensitivity with external reference weights may then be performed less frequently. This fact also is reflected by an important statement of the US Food and Drug Administration: "For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature."[11]

## Conclusion

By implementing Good Weighing Practices as a methodology to provide a risk-based life cycle approach for evaluation, selection, and routine testing of balances, measurement errors can be reduced and reliable weighing processes can be realized.

For a specific weighing process, two key issues are to be considered for a successful selection of weighing instruments:

- The weighing capacity must be larger than the largest gross load expected to be weighed by the user.
- The minimum weight of the weighing instrument for the accuracy required must be smaller than the smallest sample expected to be weighed by the user.

To achieve periodic verification of laboratory weighing instruments within an integrated qualification approach, the following procedures should be carried out:

- calibration by authorized personnel (a service technician, for example)
- routine tests to be carried out by the user
- automatic tests or adjustments affected by the instrument

The testing procedures and corresponding frequencies are based on:

- the required weighing accuracy of the application

*Concludes on page 58.*

- the severity of impact (e.g., on business, consumer and environment), in case that the weighing instrument should not deliver the correct weighing result (malfunction)
- the detectability of such a malfunction

The recommended test frequencies are increased with higher accuracy (i.e., more stringent requirements) and with increasing severity of impact, and are decreased with detectability of a malfunction. On the other hand, for less stringent process requirements and reduced risk, test efforts can be reduced accordingly. This strategy reflects current thinking about implementing a risk-based approach in qualification and validation activities.[12,13]

An understanding of the weighing process requirements together with an understanding of the basic principles of balance properties as weighing uncertainty and minimum weight enables the user to realize an integrated qualification strategy as a basis for achieving qualified weighing processes. Risk- and life cycle management thereby form an integrated part of an overall strategy to bridge the gap between regulatory compliance, process quality, and cost consciousness.

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## About the Authors


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HVAC systems can be critical systems that affect the ability of a pharmaceutical facility to meet its objective of providing safe and effective product to the patient. The ISPE Good Practice Guide on HVAC provides designers and the project team with suggestions to help determine the user requirements and the functional design that define the facility's objectives. It also provides options to be considered in creating a design that has low lifecycle cost and that is sustainable.

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# Pharmaceutical Manufacturing: How to Understand the Process and Assess the Risks to Patient Safety

by Robert Jones

**This article reviews the latest FDA philosophy to enhance and modernize the regulation of pharmaceutical manufacturing and product quality, which is perhaps best captured in two mottos: "Know Thy Process" and "Know Thy Risk."**

## Introduction

At the entrance to the Temple of Apollo, at Delphi, there was a famous inscription, commonly translated as, "Know Thyself." It was adopted by the philosopher Socrates (470 BC – 399 BC) as his motto. Easy to state, but difficult to achieve, it has been the central challenge to western philosophical thought ever since. If you don't "understand" yourself, what chance is there of achieving a meaningful existence? Philosophers, spiritual leaders, and self-help gurus have been providing us with guidance ever since on how to reach this enlightened state.

In recent years, the FDA has adopted a new philosophy designed, among other things, to free the pharmaceutical industry from its shackles and stimulate innovation by enhancing and modernizing the regulation of pharmaceutical manufacturing and product quality.[1] The challenge is for the pharmaceutical industry to demonstrate a deep understanding of its processes and the risks involved. Its philosophy for achieving this is perhaps best captured in not one, but two mottos: "Know Thy Process" and "Know Thy Risk."

The first part of this article reviews the drug development process and the methods available for "understanding" a drug manufacturing process. The second part discusses the concept of "risk" and our attitudes toward it. It provides an overview of the methods available for identifying hazards and evaluating the risks to a patient in a drug manufacturing process and discusses the question "when is the risk acceptable?" It advocates the use of Probabilistic Risk Assessment (PRA) in Quality Risk Management (QRM), which is not widely practiced within the industry at present.

Twenty-two years ago the banking industry was deregulated and revitalized, a process that was dubbed, "The Big Bang." The onus was on the banks to assess their risks and manage their business appropriately under the watchful eyes of the regulators. The result has been the near total collapse of the global financial system. Is this new FDA initiative the pharmaceutical industry's Big Bang and will our industry fare better?

## The Drug Discovery and Development Process

The process of drug discovery and drug development is a business, organizational, and regulatory process. Some estimates[28] put the cost of bringing a drug to market at $500 million to more than $2 billion and taking on average 12 to 14 years depending on the therapy or the developing firm; although in special cases, such as drugs to beat AIDS, the FDA has encouraged a fast-track process. The regulators seek to ensure that all drugs brought to market are safe and effective. Why is the drug discovery and development process so expensive and why does it take so long? Well, for every 10,000 New Drug Entities (NDEs) identified during the drug discovery process, about five are considered safe, following pre-clinical evaluations, for testing in human volunteers. Following a further seven years of clinical testing in patients and an 18 month FDA review, only about one NDE out of the five will gain approval as a marketed drug treatment.[26] The development process for new medicines typically proceeds as shown in Table A. There are many excellent sources of detailed information on this process.[3,4,5]

A great deal of effort has been expended in the last few years to streamline regulatory

*Continued on page 26.*

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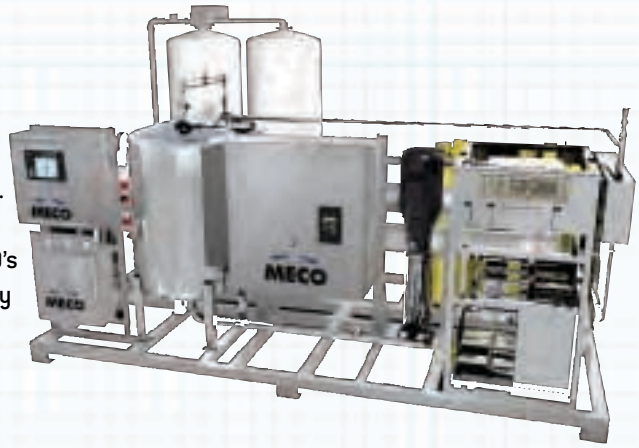


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submissions. If pharmaceutical companies submit their information in a standard format, it should be easier and therefore quicker for the regulators to review it. This should result in less recycle. The culmination of this effort is the Common Technical Document.[6]

In addition to specialists in biology and therapeutic chemistry, the discovery of a new drug involves the collaboration of pharmaceutical R&D specialists and clinical research teams composed of doctors, pharmacists, nurses, chemists, and other health specialists. Efficient information and knowledge management can potentially save valuable years and millions of dollars associated with the drug discovery and development process and a collaborative approach among these professionals can accelerate the process of expediting and approval of new drug entities. Herein lies one of the biggest opportunities to cut costs, but it does require great business vision and leadership.[7]

Another approach to improve efficiency is the recognition that the many steps in the process require different levels of experimentation. The early phase of drug discovery has components of real innovation, components of experimentation, and components that involve set routines. This model of innovation, experimentation, and commoditization ensures new ways to do work are adopted continually and allows disciplines to use appropriate internal and external resources for the right work.[8]

## Taking a Drug into Full-Scale Production

What Table A does not address is the development and scale-up of the laboratory drug manufacturing process to

**Target Identification**
Drugs normally act on cellular or genetic chemicals in the body, known as targets, which are believed to be associated with disease. Research scientists will identify and isolate a target to learn more about its functions and their influence on disease. New Drug Entities (NDEs) are then identified that interact with the target in ways that are helpful in treating a specific disease.

**Target Prioritization/Validation**
Those targets most likely to be useful in the development of new treatments for disease are selected. Tests take place to confirm that interactions with the drug target are associated with a desired change in the behavior of diseased cells and compounds can then be identified that have an effect on the target selected.

**Lead Identification**
Lead compounds or substances are those believed to have potential to treat disease. Scientists compare known substances with new compounds to determine their likelihood of success. Leads are often developed as collections, or libraries, of individual molecules possessing properties needed in a new drug. Testing is done on each molecule to confirm its effect on the drug target.

**Lead Optimization**
Here the properties of various lead compounds are compared in living organisms (in vivo) and in cells in the test tube (in vitro) to see how they are metabolized and affect the body; this allows the pharmaceutical and biotechnology companies to select those compounds with the greatest therapeutic potential.

**Pre-Clinical Technology**
Extensive laboratory development tests are carried out on the investigational drug in living organisms (in vivo) and in cells in the test tube (in vitro).

**Chemistry Manufacturing and Controls (CMC)/Pharmaceutics**
A multi-discipline team take the results of the pre-clinical testing and determine how best to formulate the drug. Regulatory agencies require testing that documents the physicochemical properties - chemical composition, purity, quality, and potency of the active ingredient and of the formulated drug.

**Pharmacology/Toxicology**
Pharmacological testing determines the effects of the investigational drug on the body and toxicology studies identify potential risks to human beings.

**Investigational New Drug Application**
Investigational New Drug (IND) in the US, Clinical Trial Exception (CTX) in the UK, and Clinical Trial Authorization (CTA) (in Australia) are examples of requests submitted to the appropriate regulatory authority for permission to begin clinical testing in humans. The regulators require that all test results are provided with the application for their review.

**Independent Review Board**
In addition to permission from the regulator, an institutional or independent review board or ethical advisory board must approve the test protocol, as well as the consent documents that volunteers sign, prior to participation in a clinical study. This process seeks to ensure that the trial is ethical and the rights of study participants are protected.

**Clinical Studies**
Clinical testing is performed in stages with increasing numbers of patients tested in each successive stage:

***Phase I Clinical Testing***
Typically takes six to nine months. These are the first studies conducted in humans and about 20 to 100 healthy volunteers take the investigational drug for short periods. The objective is to verify the safety and tolerability of the candidate drug in humans.

***Phase II Clinical Testing***
Typically takes from six months up to three years. Testing is conducted on several hundred patients suffering from the condition the investigational drug is designed to treat. The objective is to determine effectiveness and safety in patients.

***Phase III Clinical Testing***
Typically takes between one and four years. Testing is conducted on thousands of patients. The objective is to determine expanded effectiveness and safety in patients.

**New Drug Application**
New Drug Application (NDA) in the US and Marketing Authorization Application (MAA) in the UK are examples of applications submitted to the appropriate regulatory authority for permission to market a new drug. The regulators require that all information collected during the drug development process is provided with the application for their review. The application must present convincing evidence that the drug will have its stated effect when used under the prescribed conditions. The regulatory body may inspect the facilities where the drug will be manufactured. This stage of the approval process can take between six months and two years.

**Additional Clinical Studies**
Before and after the regulator has approved a drug, pharmaceutical companies may conduct additional late stage studies, which can last from several months to several years:

***Phase III Clinical Testing***
Some extended Phase III trials often begin, while the regulatory submission is pending, to provide additional safety data, or test the drug for additional conditions for which it may prove useful. Some companies call these Phase IIIb studies.

Phase IV studies expand the testing of an approved drug to broader patient populations. The long term effectiveness and the cost of the drug compared to alternatives.

**Post Approval Studies**
These studies test a marketed drug on new age groups or patient types or they may investigate previously unexpected side effects or related risk factors.

Table A. The drug approval process.

*Continued on page 28.*

a full-scale production. Figure 1[9] shows in block form the technology transfer process. This is the process of taking the drug substance, the drug product, and the analytical tests and methods from the R&D sites to the commercial manufacturing site. It is in this area where most of the ISPE membership is probably involved.

The cost of getting technology transfer wrong is enormous. A product that is six months late getting to market can lose out on a significant percentage of the estimated profit over the product's lifecycle.

Technology transfer also means transferring all the associated knowledge, information, and skills from R&D to be able to manufacture the drug substance and drug product in full-scale production. In the past, this process has sometimes been problematic and inefficient, due to poor knowledge management. Much of the knowledge gained in early studies was not transferred to the process chemists and process engineers, resulting in delays downstream in getting the production plant commissioned and the process operating and validated.

## Quality by Design

In an attempt to improve this state of affairs the regulators and industry in the International Conference on Harmonization (ICH) process, have adopted the principle of Quality by Design (QbD).[10, 27] This is a means of assuring the quality of a drug as it relates to its safety and efficacy. In practice, this means that the product's Critical Quality Attributes (CQAs) and CQAs of drug substance, excipients, intermediates (in-process materials), and Critical Process Parameters (CPPs) impacting on drug product CQAs should be identified and characterized. The CQAs must be controlled within an appropriate limit, range, or distribution to ensure the desired product quality and a CPP is a process parameter whose variability has an impact on a critical quality attribute; therefore, should be monitored or controlled to ensure the process produces the desired product quality. We need to know by how much we can vary the product formulation, manufacturing operating parameters, and raw material quality and still maintain acceptable product quality. This region of acceptable variability could be represented as a Design Space, which is defined as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Outside of these ranges lies the boundary layer where predictions of product performance are uncertain. With this knowledge, engineers can set control ranges for the critical instruments (i.e., those deemed to impact on CPPs and CQAs) on the plant within which acceptable product quality and performance is assured. It also is necessary to assess the impact of each process step on product quality. This helps minimize the subsequent validation effort of *Continued Process Verification*.[33] To achieve this, we need to explore every detail that might impact on product quality, using sound science, a risk-based approach, and common sense. Effort can then be focused on those areas that have a significant impact.

This more substantial development and process optimization effort, providing greater process understanding based on solid science and risk management, has important business and other benefits.[31] It means that improvements of the process or product that do not affect product quality could potentially be made without post-approval submission to the regulatory body which would otherwise slow the process down considerably.

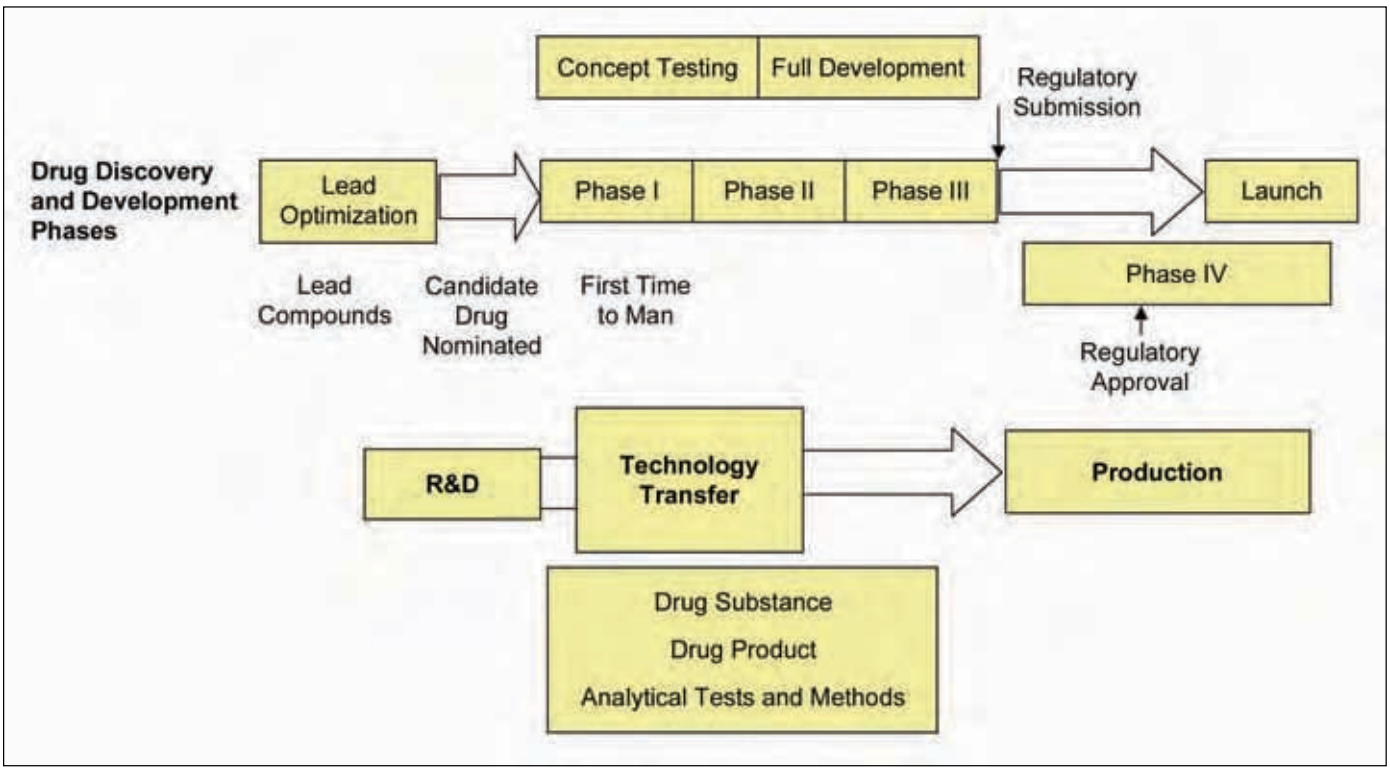


Figure 1. The drug discovery and development process and technology transfer.

*Continued on page 30.*

# **Scale-up –** Lab to Production

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**Single-use Dosing System**
The PreVAS system offers a cost effective dosing system that can evolve with your product as it goes through clinical trials to production. The flexible design of the dosing system allows expansion without changing dosing principles, technologies, methods, or introducing new product contact parts. This ability to stay with one accurate dosing system from clinical filling to development and through production can greatly reduce validation hurdles and shorten market introduction time.

**PreVAS Advantages**
PreVAS systems are the industries first single-use dosing systems designed to take full advantage of the Rolling diaphragm pump which offers a highly accurate dose over time and has gentle product handling characteristics. PreVAS systems are tailor made to your specifications including all tubing pumps, filling needles fittings and intermediate product bags. Systems are delivered with a prevalidation package, fully assembled, and sterilized for immediate use.

**Lab Scale Vial Filler**
The FLT is a small scale, 30 vial per minute, vial filling system designed to offer features similar to a full scale filling system. The FLT offers a wide variety of options including over gassing, stoppering, capping, barrier systems, and check weighing on one machine reducing labor, risk and product loss. Minimal size parts, simple operation and rapid change over increase versatility.

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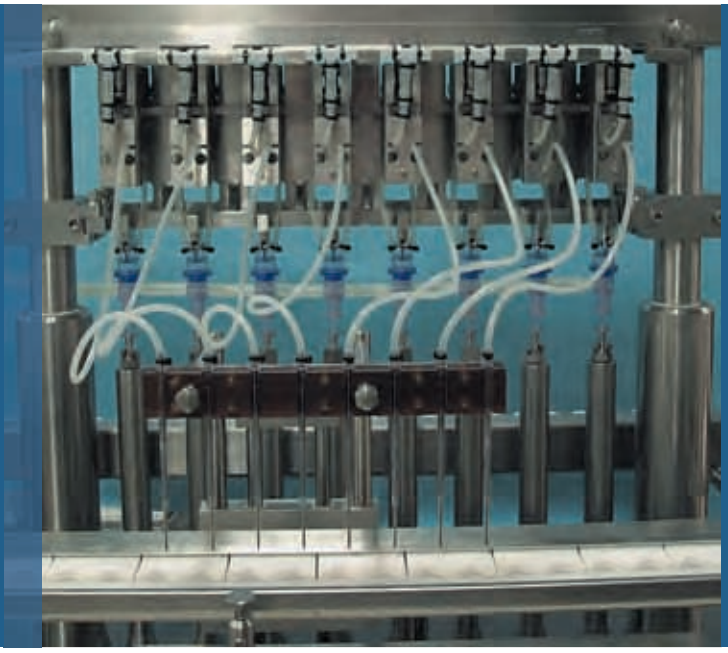

QbD involves thinking ahead ("begin with the end in mind"). It requires a clear roadmap for product development and preparation for technology transfer. It requires more resource to be applied earlier in the drug development phase. It also requires the use of technologies that support better knowledge management to allow us to gather, store, and retrieve knowledge and share it within teams and across our organizations so that it can be fully utilized in the continuous improvement of our products and processes. This would help to eliminate the need to over-design facilities and would enable focused risk-based verification of suitability and fitness for purpose of the process plant.

## PQLI

The ISPE Product Quality Lifecycle Implementation (PQLI) initiative was launched in June 2007[29] to help industry find practical approaches to the global implementation of recent quality guidelines published by the International Conference on Harmonization (ICH),[11,22,30] which includes an understanding of QbD principles.

## Understanding the Process

Some of the major advanced methodologies and technologies that can help to achieve a comprehensive process understanding are discussed below and references are given to more detailed sources of information. Large pharmaceutical majors have most of these methodologies and technologies in-house, but smaller pharmaceutical companies can now access these through specialist organizations.[11]

**Design of Experiment (DoE)** is a method used to determine the relationship between the different factors affecting a process and the output of that process. This method was first developed in the 1920s and 1930s by Sir Ronald A. Fisher. With the advent of modern desktop computing power, sophisticated software packages, and expert consultancies, these techniques are now available to every company.

Experimental design can be applied whenever we need to investigate a phenomenon in order to gain understanding of, or improve, performance.

To build a design we carefully choose a small series of experiments that are to be performed under controlled conditions. There are four interrelated steps in building a design.[12]

1. Define an objective to the investigation, e.g., "better understand" or "sort out important variables" or "find optimum."
2. Define the variables that will be controlled during the experiment (design variables) and their levels or ranges of variation.
3. Define the variables that will be measured to describe the outcome of the experimental runs (response variables) and examine their precision.
4. Among the available standard designs, choose the one that is compatible with the objective, number of design variables and precision of measurements, and has a reasonable cost.

Standard designs are well-known classes of experimental designs. They can be generated automatically as soon as we have decided on the objective, the number and nature of design variables, the nature of the responses, and the number of experimental runs we can afford. Generating such a design will provide us with a list of all experiments we must perform, to gather enough information for our purposes.

DoE is widely used in research and development, where a large proportion of the resources go toward solving optimization problems. The key to minimizing optimization costs is to conduct as few experiments as possible. DoE requires only a small set of experiments and thus helps to reduce costs.

Areas where DoE is used in industrial research, development, and production include:

- optimization of manufacturing processes
- optimization of analytical instruments
- screening and identification of important factors
- robustness testing of methods
- robustness testing of products
- formulation experiments

**Multivariate Data Analysis (MVA)** refers to any statistical technique used to analyze data that arises from more than one variable. This essentially models reality where each situation, product, or decision involves more than a single variable. The information age has resulted in masses of data and the ability to obtain a clear picture of what is going on and make intelligent decisions is a challenge. When available information is stored in database tables containing rows and columns, MVA can be used to process the information in a meaningful fashion. With MVA, we can:

1. Obtain a summary or an overview of a table. This analysis is often called Principal Components Analysis or Factor Analysis. In this overview, it is possible to identify the dominant patterns in the data, such as groups, outliers, trends, and so on.
2. Analyze groups in the table, how these groups differ, and to which group individual table rows belong. This type of analysis is called Classification and Discriminant Analysis.
3. Find relationships between columns in data tables, for instance relationships between process operation conditions and product quality. The objective is to use one set of variables (columns) to predict another, for the purpose of optimization, and to find out which columns are important in the relationship. The corresponding analysis is called Multiple Regression Analysis or Partial Least Squares (PLS), depending on the size of the data table.

**Process Analytical Technology (PAT)**[13] is an approach that is intended to support innovation and efficiency throughout the product lifecycle. It consists of a set of tools and principles (including MVA) for understanding and controlling the manufacturing process. It can be used to define the CPPs, which as mentioned above, are those process variables which need to be controlled to maintain the CQAs. The power of this tool is that it is possible to:

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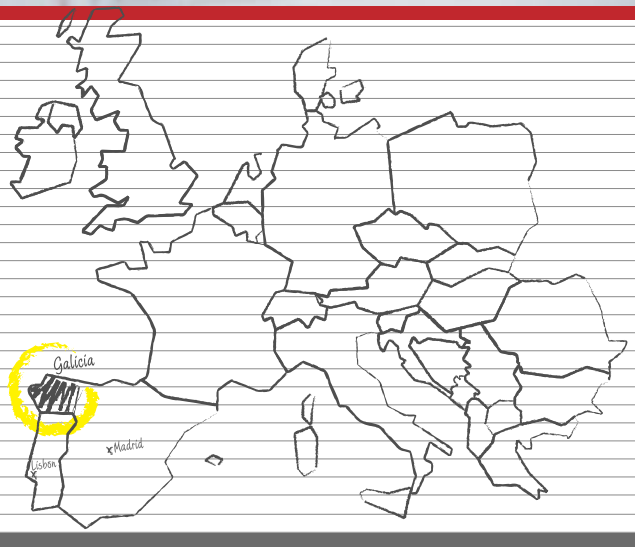


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- Help determine a parameter or attribute which contributes to "real time release testing"; the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.
- Monitor some parameters on line or at line.
- Conduct sensitivity analyses to determine the impact of process deviations on the product's CQAs.
- Monitor and control the process endpoint and for continuous improvement.
- Generate mathematical relationships promoting process understanding.
- Enable real-time monitoring and ultimately, real-time release.

PAT can be applied effectively to batch processes, but the greatest benefits are obtained when it is utilized with continuous processes, which are finally starting to make inroads into pharmaceutical production.[14]

**Process Modeling** "is the art or activity of building a mathematical model of the process (or a product, for that matter) by describing its fundamental physical and chemical relationships – without specifying how they are to be solved."[15]

Groundbreaking general purpose process modeling tools now allow a highly accurate model of a chemical process to be built. With such a process model, it is possible to perform all the activities required to model across the process lifecycle, from conceptual design and laboratory experimentation through detailed engineering design to operation. We can:

- **Perform simulation runs** (steady state and dynamic) to see what happens if feed conditions are varied.
- **Estimate parameters** using model-based data analysis and validation techniques and comparing these against experimental data. This can enhance predictive accuracy significantly and provides information that can be used in formal risk analysis.
- **Design experiments** to refine the parameter estimations and reduce the risk associated with measurement inaccuracy.
- **Perform optimizations** – dynamic or steady-state – on the model, to directly calculate optimal trajectories or values rather than undertaking lengthy trial-and-error investigations.
- **Generate linearized models** for use in control design applications or Model-based Predictive Control (MPC), gain scheduling or any other activity that requires linear models.
- Because this is a model and not a simulation, **simulate "backward"** to find out what feed or unit values give rise to the desired product qualities, at no additional cost in terms of execution time or complexity of model.
- **Generate an Equation-Set Object (ESO)** for other software – for example, plant-wide optimizers – to use.

By way of example, **Process Control** of bioreactors is difficult, due to their non-linear dynamic behavior and the fact that the model parameters vary in an unpredictable manner. This complexity inhibits accurate modeling. The lack of suitable sensors makes the process state difficult to characterize, but continuous processing is desired in order to optimize throughput. There are a number of techniques available for the non-linear control of processes, e.g., differential geometric approach, reference synthesis technique, predictive control design, etc., but their major disadvantage is the computational time required to perform the prediction optimization. Recently, researchers using a nonlinear controller,[16] based on a polynomial discrete time model (NARMAX), have extended its use to fermenters and report satisfactory results.

**Britest**[17] is a not for profit company directed by its members; a consortium of manufacturing companies (including pharma), major engineering contractors, and top universities. The aim of Britest is to improve processes, both chemical and physical, from conception to operation; to apply effort where it will give most benefit; to leverage existing knowledge to maximum effect; to identify important gaps in our knowledge and produce a targeted program of experimentation.

This is achieved using the Britest Toolbox, a set of tools to help groups structure their thinking. This works alongside other tools, such as DoE, etc. Most tools tend to be used by a team with a facilitator guiding the group as follows:

1. Start with an overview of the business case.
2. Review the whole process.
3. Identify where most benefit is to be gained.
4. Analyze those areas in detail.
5. Find where data is missing/not well understood.
6. Experiment/research to obtain missing data.
7. Include data in the analysis and complete the model.
8. Use the model to underpin decision making.

It is all about knowledge management. In order to achieve true process understanding, many disciplines are involved. Bringing these disciplines round a table in interactive discussion, pooling knowledge, and facilitating group conceptualization is what Britest is about. It is an effective tool for QbD. Britest's process understanding development philosophy is shown in Figure 2.

**Visual Literacy**[18] is the ability to evaluate, apply, or create conceptual visual representations for communicating new knowledge and devising new ways of representing insights. There are some wonderful tools at the Visual Literacy Web site, including a Periodic Table of Visualization Methods.[19] This is a compilation of 100 existing visualization methods compiled using the logic, look, and use of the periodic table of the elements. As they say, a picture paints a thousand words!

**Modeling and Decision Support Tools.** A useful Web site that refers to many useful tools that can be employed in the service of process understanding is courtesy of the Institute for Manufacturing at the UK's Cambridge University,[20] which lists them alphabetically and also under the headings of: Information Control, Paradigm Models, Simulation Models, Ways of Choosing, Representation Aids, and Processes.

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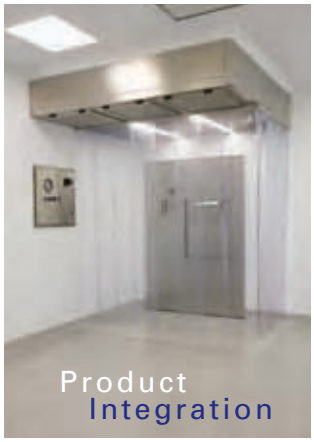



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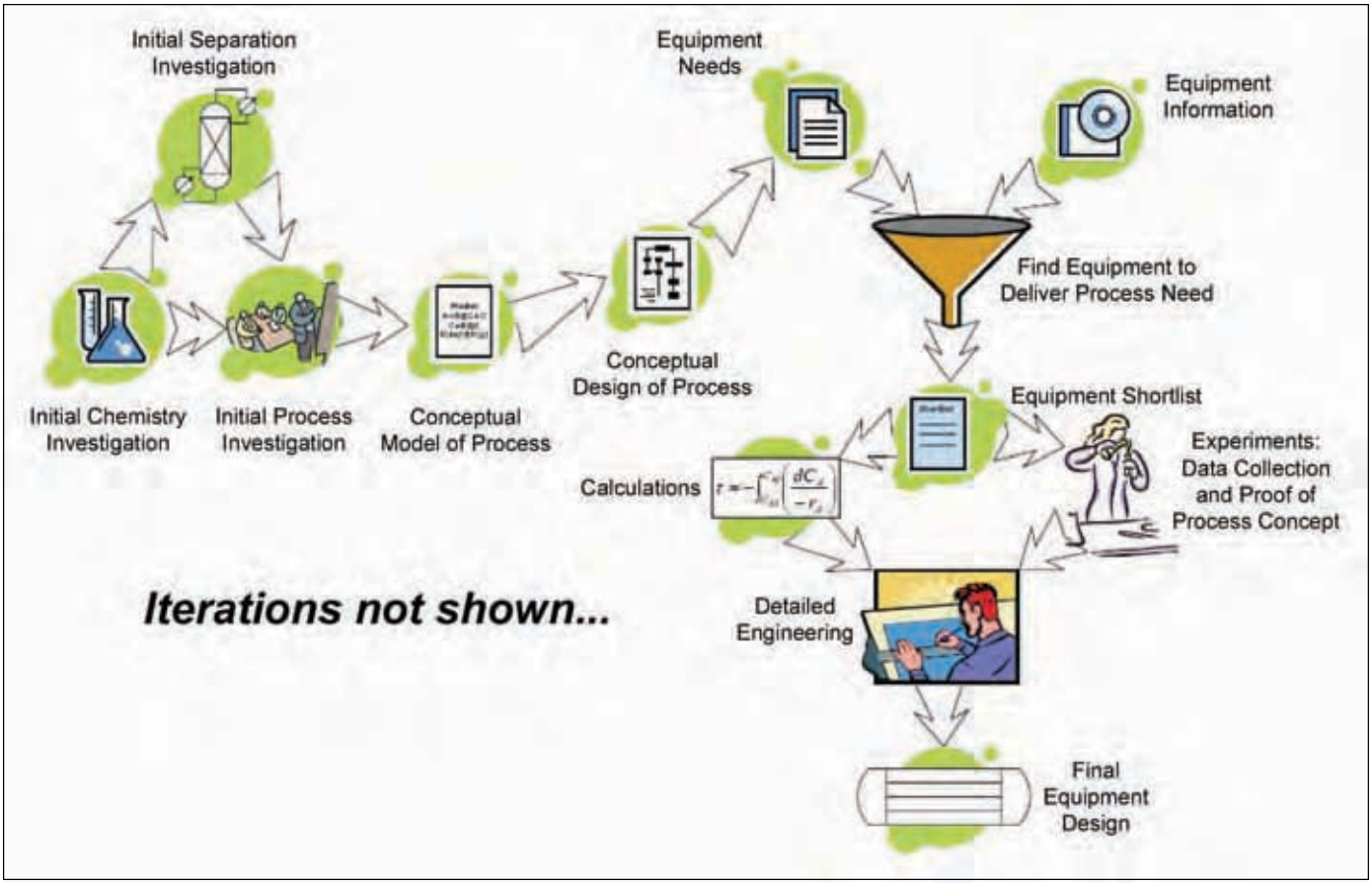


Figure 2. Process understanding development philosophy.

The above discussion has highlighted the many tools available for understanding our processes. The technological landscape has never been more exciting; technology and new techniques are developing rapidly and there has never been a better time to "Know Thy Process."

## Introduction to Risk Management

The latest FDA philosophy advocates a risk-based approach to, among other things, "encourage the early adoptions of new technological advances by the pharmaceutical industry."[1]

Whether we like it or not we are all gamblers in the game of life. From the moment of conception, we are exposed to hazards; from nature, from the environment, from other people, from other creatures, and from ourselves and our creations. We have absolutely no control over some hazards: some we can totally control. However, in many cases, hazards can be mitigated, but not completely removed.

Risk management is important for us all as individuals and for our organizations. In the old days, when life was not so busy, we did not dwell too much on unhappy possibilities. Fire and crossing roads were perceived to be significant hazards and we were taught to take sensible precautions. There was not so much forward thinking, and in due course, accidents would happen, lessons would be learned, and we would start again with a revised set of precautions in place.

The rapid pace of change in the development of drugs, technology, and communications has led to organizations undertaking increasingly complex and ambitious projects. This complexity and the change of pace require a very formal forward-looking approach to risk management. The recent problems with Heparin[21] have clearly demonstrated that in complex supply chains, there is uncertainty, lack of knowledge, and the potential for rare, high-consequence outcomes. The good thing for the life sciences industry as far as risk management is concerned is that all the hard work has been done by other industries, namely, aerospace, nuclear, and the hydrocarbons industry. They have come up with sophisticated techniques to manage their risk. The challenge is how to take this knowledge on board and apply it to our own system of Quality Risk Management as defined in the guidance for industry, ICH Q9, which has been adopted by the FDA and the EU.[22]

We must have some means of estimating the probability of failure of the elements of drug manufacturing systems to allow a manufacturer to focus attention and limited resources as effectively as possible on the most critical systems.

Risk management involves:

1. Identification of the risks.
2. Evaluation of the risks.
3. Control of the risks.
4. Financing the decisions.

In this article, we are focusing on Identification and Evaluation of the risks.

## Risk Assessment Techniques

The latest, most sophisticated technique available for risk assessment is **Probabilistic Risk Assessment (PRA)**, which was once deemed too "difficult," but has now reached a mature stage in its development. This technique is not widely used in the pharmaceutical industry at present, but there is an awareness that it may be useful in the design of complex pharmaceutical molecules, such as monoclonal antibodies.[2]

Sometimes risk is defined as the expected value of an undesirable consequence. However, this is only a summary measure and a probability distribution for the consequence affords a much more detailed description of risk. Determining risk generally involves answering the following questions:

1. What can go wrong?
2. How likely is it?
3. What are the consequences?

The answer to the first question is a set of accident scenarios. To answer the second question we need the probabilities of the scenarios and for the third an estimate of their consequences. This definition emphasizes the development of the accident scenarios and makes them a part of the definition of risk. The scenarios are one of the most important results of the risk assessment.

PRA begins with a set of "Initiating Events" (IEs), which impact the system, causing it to change its operating state or configuration. For each IE, the analysis proceeds by determining the additional failures that may lead to undesirable consequences. Then the consequences of the scenarios are determined, as well as their frequencies, and finally they are put together to create a risk profile of the system, which supports risk management. Figure 3, borrowed from NASA, shows the implementation of these concepts in PRA.[23]

PRA studies often require special analysis tools, such as Human Reliability Analysis (HRA) and Common Cause Failure (CCF) analysis. HRA deals with methods for modeling human error (which are deemed to be the largest contributors to sterility failure in aseptic processing). CCF deals with methods for evaluating the effect of inter-system and intra-system dependencies, which tend to cause simultaneous failures and thus significant increases in overall risk.

PRA studies should be performed:

- when information is not sufficient to comprehensively assess strengths and weaknesses of complex systems by other means
- when important complex jobs must be performed successfully for the first time
- in all lifecycle phases of a complex system

An integrated PRA has its own value that is greater than the sum of its parts. Some of the benefits of an integrated PRA are:

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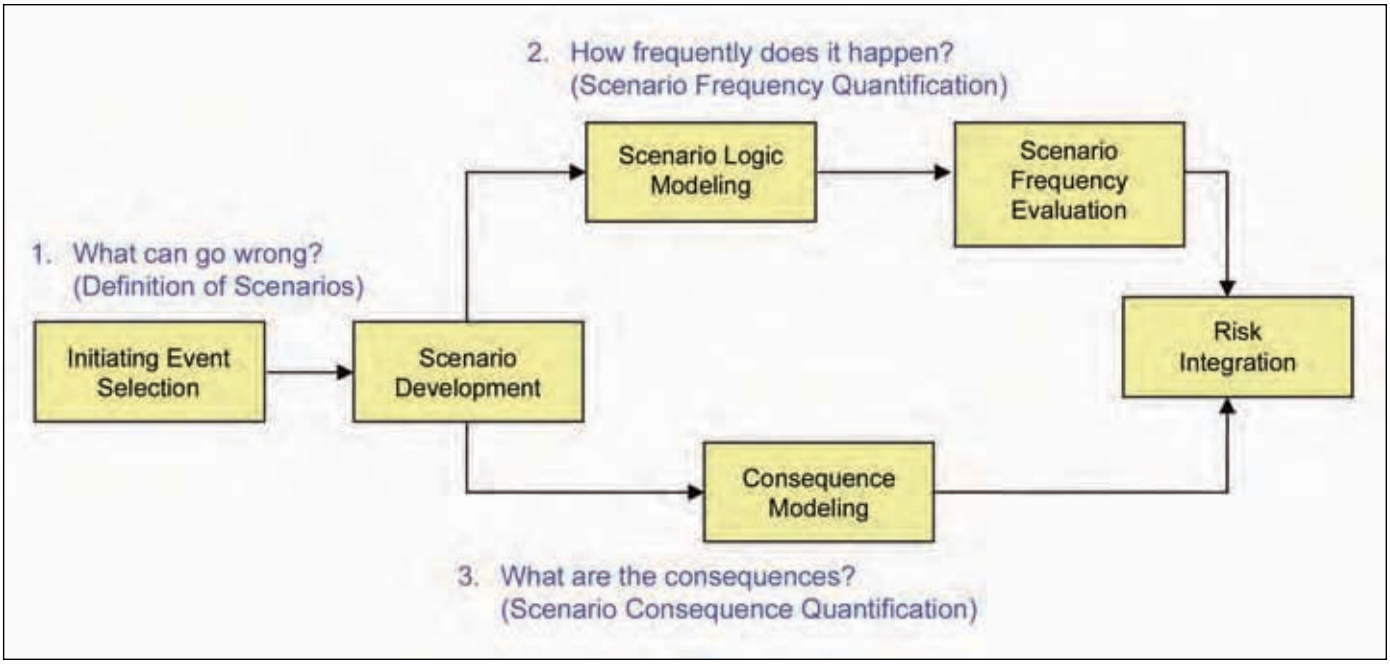


Figure 3. Implementation of risk assessment using PRA.

- The model configuration can be kept aligned with the system configuration.
- Facilitates "what if?" analyses for proposed design changes and upgrades.
- Provides basis for risk-based maintenance.
- Provides basis for risk-based decision-making.
- Captures the knowledge of experts.

Some of the benefits of the numerical results of PRA are:

- Enables us to respond to those who demand "give me the numbers."
- Allow us to express the uncertainty in our state of knowledge – a gap analysis.
- Comparison of risks with risks "acceptable" to society.
- Provide relative ranking of "risk drivers" and show where to concentrate our limited resources for maximum risk reduction.

To make comparisons of the risks of different activities, risk analysts use the term micromort, which is a one-in-a-million chance of dying. According to the United Kingdom Rail Safety and Standards Board, the average person experiences a micromort by:

- driving 230 miles in a car
- riding six miles on a motorbike
- traveling 6,000 miles in a train
- taking three flights

So what about the traditional methods of risk assessment?

Failure Modes and Effects Analysis (FMEA) and Hazard Analysis are useful as inputs to a PRA, but do not meet the full requirements of the PRA as they do not take account of dependencies and multiple failures. They only show worst case consequences and so cannot provide total probabilities of end states with uncertainties. Hazard analyses, if available, are useful as inputs for identifying initiating events and scenarios and FMEAs are useful in checking Fault Tree basic events. Interface FMEAs are useful in checking functions that need to occur for system success. If FMEAs or Hazard Analyses are not available, a PRA will substitute for them because all the information will be there, albeit in a different form, providing the analysis is complete. PRAs are essentially linked Fault Trees. If appropriate, portions of a Fault Tree Analysis (FTA) can be used as part of the PRA, but it is difficult to split the PRA into many different trees with different top events and qualitative Fault Trees are very different to quantitative ones. Fault Trees do not show time or sequences. In summary, the FTA supports the PRA, not vice versa.[24]

While the mathematics can become complicated, PRA software is available to speed up the process. The two most well-known examples are:

- Quantitative Risk Assessment System (QRAS) – developed for NASA by the University of Maryland.
- Systems Analysis Program for Hands on Integrated Reliability Evaluations (SAPHIRE) – developed for the US Nuclear Regulating Commission.

It is said that during the early Apollo project the question was asked about the probability of successfully sending astronauts to the moon and returning them safely to Earth. Some sort of risk calculation was performed and the result was 0.2, a very low probability of success. This discouraged NASA from performing quantitative risk analysis. NASA pushed on regardless and five successful moon missions out of six attempts did not imply any need for PRA. Instead,

NASA relied on FMEA for system safety assessments, which continue to be a requirement by NASA to date in all its safety related projects.

On 28 January 1986, after 25 successful flights, the Space Shuttle Challenger exploded. The resulting investigation by the US House of Representatives, concluded: "Without some means of estimating the probability of failure of the various [shuttle] elements it is not clear how NASA can focus on the most critical systems." Later the Slay committee said: "The committee recommends that probabilistic risk assessment approaches be applied to the shuttle risk management program at the earliest possible date. Databases derived from Space Transportation System (STS) failures, anomalies and flight test results, and the associated analysis techniques, should be systematically expanded to support probabilistic risk assessment, trend analysis, and other quantitative analyses relating to reliability and safety."

Since then, NASA has developed the PRA technique extensively and uses it on all its safety projects.

Figure 4 is borrowed from NASA[23] and shows the relationship between risk management, PRA, and the traditional risk assessment techniques.

In 2008, the results of a survey of quality risk management practices in the pharmaceutical, devices, and biotechnology industries were published.[25] Among the major findings are:

- The "aseptic processing/filling" operation is the functional area identified as having the greatest need for risk assessment and quality risk management.
- The most widely used methodology in industry to identify risk is FMEA. This tool was most widely applied in assessing change control and for adverse event, complaint, or failure investigations.
- Despite the fact that personnel training was identified as the strategy most used for controlling/minimizing risk, the largest contributors to sterility failure in operations are still "personnel."
- A majority of correspondents verified that they did not periodically assess their risk management programs.
- A majority of the correspondents desired to see case studies or examples of risk analysis implementations (as applicable to aseptic processing).

FMEA is a very good technique that is easy to understand and use. We should continue to use it as it is valuable for assessments carried out at component level and also is very useful in capturing knowledge. However, it will not show the "big picture" and it cannot deal with system interactions and human error in the way that PRA can.

Establishing quality risk management within the corporate culture is not easy. It must be driven by the CEO. There are subject matter experts out there with the knowledge and experience to help.

It is important to note that risk assessments rest on estimating probabilities, which is notoriously difficult. Many court rulings relating to cot deaths, DNA matches, etc., have had to be overturned on appeal, highlighting the inherent difficulty with probability-based statistical evidence provided by expert witnesses.[32]

## Summary

We are very well placed to understand our processes – better than at any other time in history. We may be able to identify all the modes of failure of our processes, but evaluation of

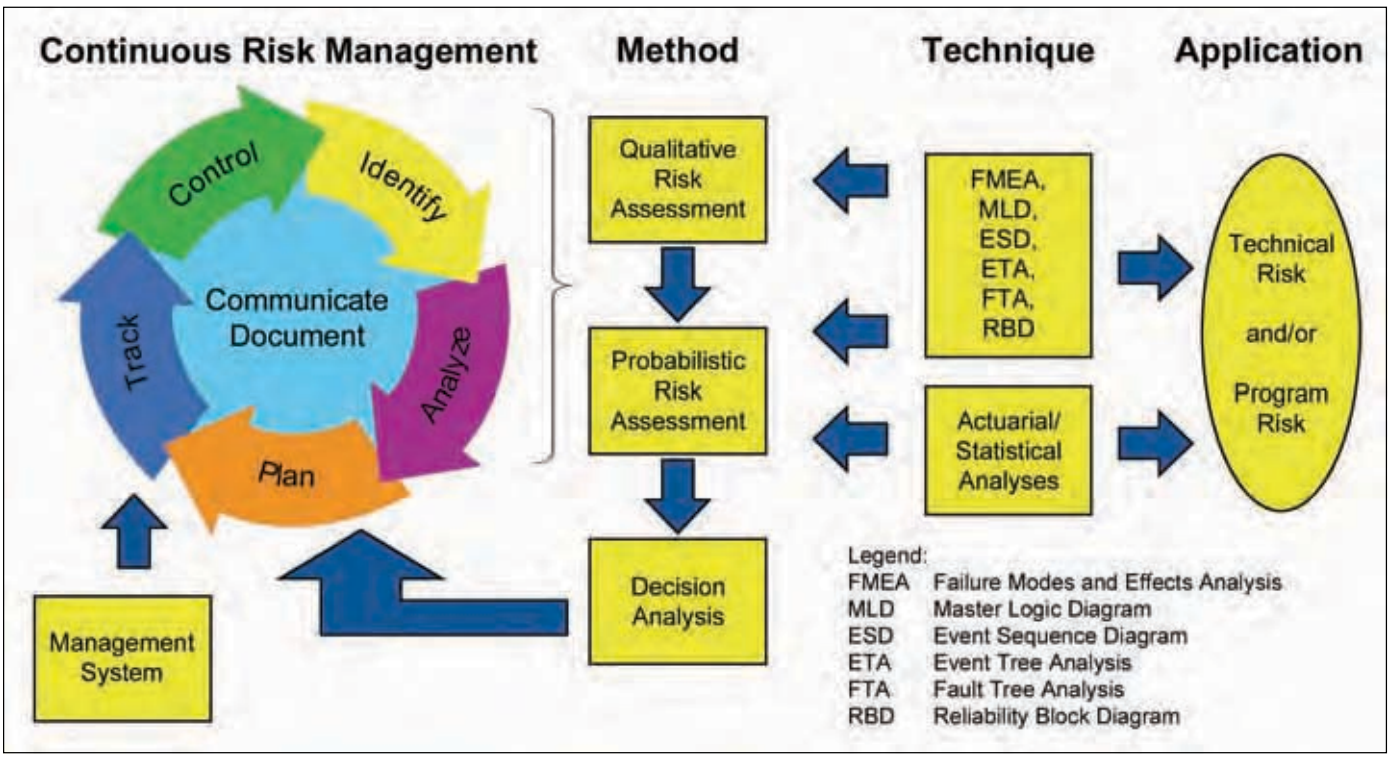


Figure 4. Relationship between risk management and Probabilistic Risk Assessment (PRA).

*Concludes on page 38.*

the risks depends on our ability to accurately assess the probabilities of failure and this is difficult. Other regulated industries, like the nuclear and aerospace industries, have suffered severe mishaps in their development, but now have mature risk management cultures. Others, most notably the financial and banking industry, have tried to manage their risk, but have been confounded by the complexity of their systems and have been brought to the brink of collapse. The pharmaceutical industry must tread cautiously and learn from the successes and failures of others.

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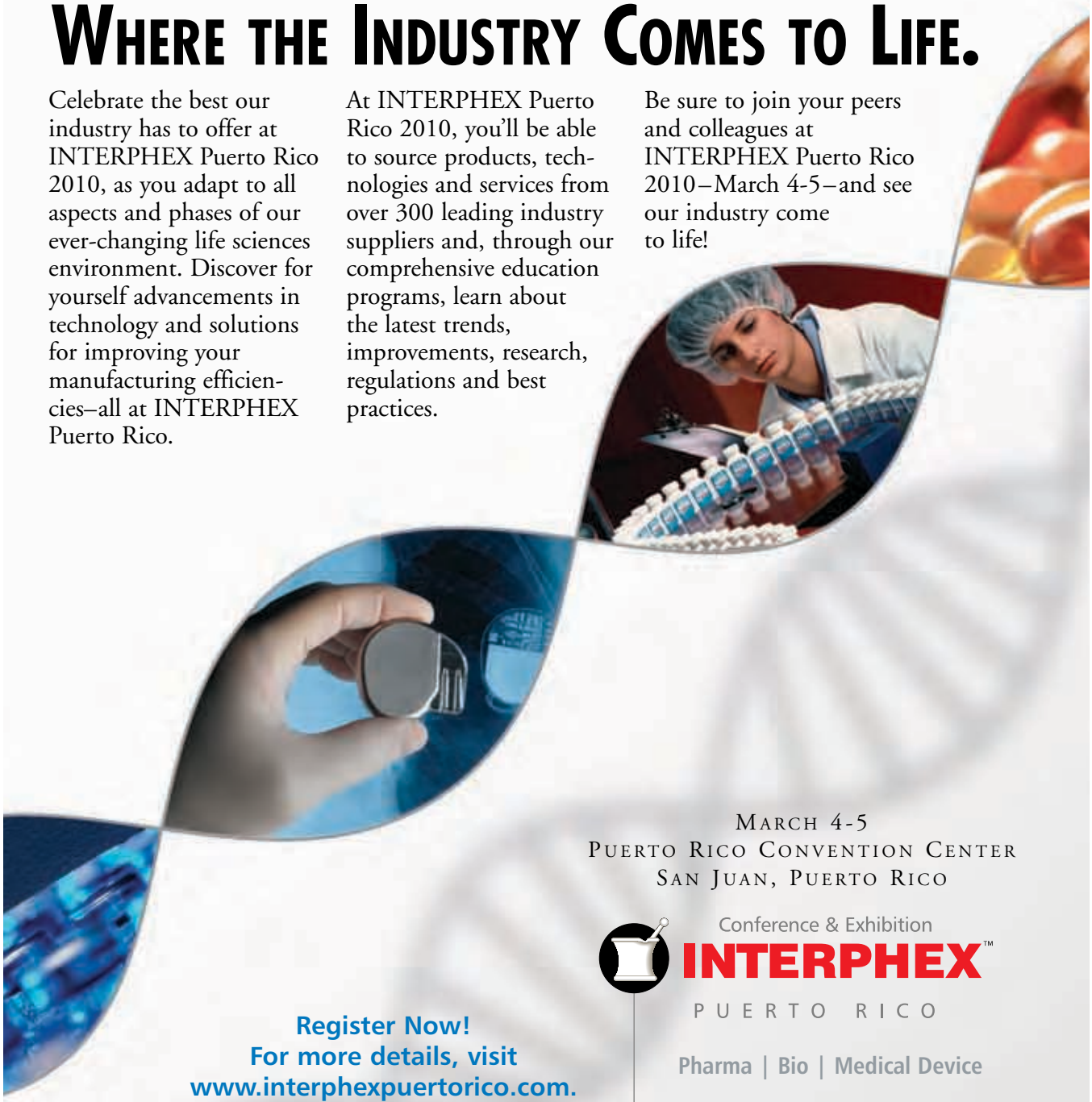

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**This article describes the approach for implementation of the ASTM E2500 standard in Pfizer to enable a cost-efficient and lean approach to science- and risk-based verification.**

# Commissioning, Qualification, and Verification – Lean Approach to Implementation

by Nicholas Andreopoulos, Gert Moelgaard, Sabra Seyer, and Graham Wrigley, PhD

When the existing ISPE Baseline® Guide for Commissioning and Qualification (Volume 5) was launched in 2001, it gained broad acceptance in pharmaceutical companies around the world and has been widely applied as the reference for a more streamlined approach compared to the older concepts of validation that were used quite differently in various companies.

The Baseline® Guide introduced a few key concepts and there have been significant improvements in the application of C&Q. Companies have established Good Engineering Practices (GEPs) and in doing so, increased the ability to leverage commissioning tests into Installation and Operational Qualification (IOQ). The impact assessments also have been very effective in identifying the manufacturing systems that have direct impact on product quality.

Many companies have realized that even today's practices of C&Q are still quite expensive and time consuming and do not focus on the opportunities afforded by a science- and risk-based approach. A significant effort has been undertaken within some companies to streamline the C&Q tools and practices, and there have been resulting improvements. With the establishment of Good Engineering Practice (GEP) and Quality Risk Management principles, there are new opportunities to rethink current practices.

In May 2007, the ASTM Committee E55 on "Manufacture of Pharmaceutical Products" approved the ASTM E2500 "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment." This was the starting point of an industry transition toward a science- and risk-based approach to Commissioning and Qualification.

ASTM E2500 changes the focus of C&Q. Where the C&Q Baseline® Guide focuses on each manufacturing system with its system and component impact assessments, the ASTM E2500 Standard enables a verification approach focused on the product/process requirements and risks to product quality and patient safety.

The E2500 standard was originally initiated by ISPE's International Leadership Forum to leverage the principles of Quality Risk Management as outlined in the Q9 Guideline from International Conference of Harmonization (ICH). Since the ASTM E2500 Standard was approved, a number of articles have been written and presentations given which has resulted in a lot of discussion on its application. It is now becoming the core content of the ISPE Baseline® Guide on Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment.

The application of the ASTM E2500 Standard and the new ISPE Baseline® Guide based on E2500 is a natural progression toward a streamlined science- and risk-based activity that ensures the 'fitness for use' of a manufacturing system in a significantly more cost-effective way than traditionally applied. 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.

## E2500 Verification as a Lean Approach

When the ASTM E2500 Standard was approved, it was seen as a major breakthrough by some

*Continued on page 10.*

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*"The term Verification was selected to enable and describe how the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk to the patient – and specifically applies it to the Verification effort."*

companies whereas other companies seemed hesitant to apply it – especially companies that were not familiar with the Quality by Design (QbD) and Quality Risk Management principles.

However, over the past year, many companies are starting to apply Quality Risk Management for new and existing products. Companies have seen what a useful tool a well conducted Quality Risk Assessment based on product and process knowledge can be. When applied to verification activities, it really helps focusing the main attention of the verification activity to those aspects of the manufacturing systems that are critical to product quality and patient safety.

Within Pfizer a lean project was established in 2007 to challenge the current C&Q approach. This project was led by representatives from the Global Engineering, IT, and Quality groups, and was sponsored by Pfizer leadership. The primary focus of the project is not just the implementation of new standards or tweaking of the current C&Q approach, but a re-evaluation of the C&Q process to have a step change improvement in cost and schedule efficiency. The intent was to continue on the C&Q enhancements that were implemented at Pfizer sites and to use the ASTM E2500 as an enabler of the next level of C&Q improvements.

The lean approach also was utilized to ensure that the issues with the current C&Q approach are addressed with the new process and to establish metrics to confirm the process improvements.

The first step of the lean project was to obtain feedback from the organization on C&Q execution issues. This defined the C&Q issues which were addressed as part of the lean project. The feedback from the organization identified important business challenges, such as:

- overall C&Q process is too complex with numerous documents, steps, and reviews
- lack of process scaleability and flexibility in the approach
- lack of integration with other systems (i.e., automation)
- lack of consistency in the application of system- and component impact assessments across the organization
- need for clarification or redefinition of roles and responsibilities in C&Q projects
- overdoing leveraged commissioning efforts because some commissioning may become part of the qualification documentation

The ASTM E2500 standard and ICH Q8/9/10 concepts can be used to address some of these issues and enable a streamlining of the C&Q process into an overall Verification program.

## ASTM Verification Approach versus Qualification

The core concept of ASTM E2500 is described with the term **'Verification.'** The standard deliberately avoided the terms *'Qualification'* and *'Validation'* to signify an intentional departure from past practices.

The term Verification was selected to enable and describe how the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk to the patient – and specifically applies it to the Verification effort.

In traditional C&Q, some companies ended up applying the rigid Qualification methods, level of documentation, and Quality Unit approval to most of their facility project documents, despite the impact assessment process. This resulted in technical details being included in large, highly prescriptive protocols and significant efforts for both Commissioning and Qualification. For those companies, the distinguishing between commissioning and qualification was lost and C&Q did not lead to the anticipated savings.

Some of the companies that have applied the C&Q method, as well as the previous GAMP approach to computer system validation, have been executing parallel programs leading to repetitive testing of the same features and functions.

The scope of Verification is broad and the approach is relying on *Good Engineering Practices (GEPs)* and other supporting principles as described in the E2500 Standard. Accordingly, the scope and extent of the verification activities where the Quality Unit should be involved are mainly in areas of potential risk to the patient safety and product quality, i.e., the Critical Aspects of the manufacturing system.

Previous C&Q practices have a missing link between the impact and the actual risk to quality, safety, and efficacy of the drug product, which the ASTM E2500 addresses. There is a need for a change, to a focus on product quality, safety, and efficacy and to a focus on a verification approach based on Good Engineering Practices, Quality Risk Management, and a few other supporting activities.

## Quality Risk Management and Verification

The key to successful Verification of a facility project is a clear Quality Risk Management approach. For *new* pharmaceutical products developed by Quality by Design (QbD) principles, this is largely done as part of product development and registration, but for *existing* products (*legacy* products), it has to be deduced from other sources, including the available process development documentation, process validation packages, and the manufacturing history.

The main focus of the Verification effort is put on the *Critical Aspects* of the manufacturing system, meaning the functions,

*Continued on page 12.*

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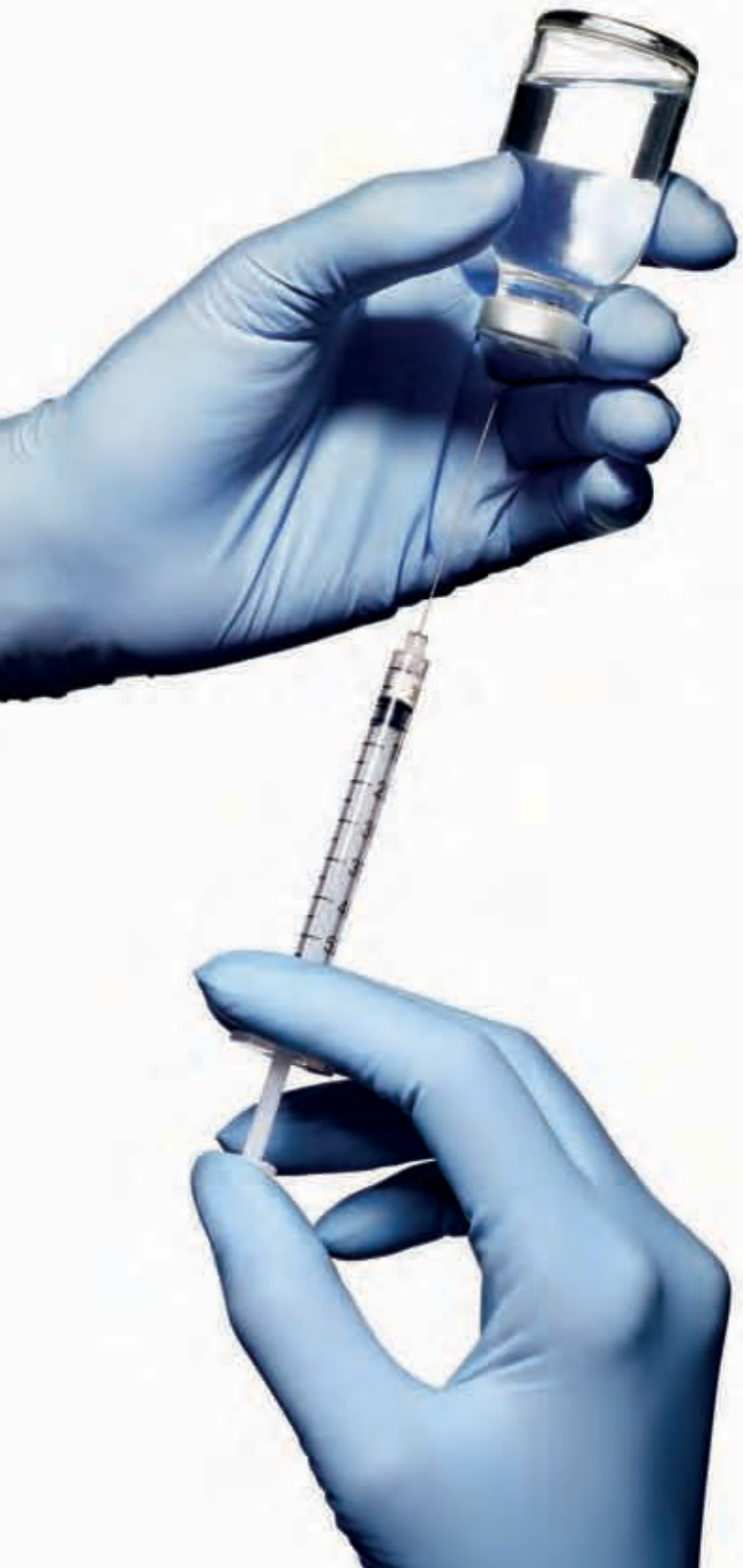

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features, etc. necessary for the manufacturing process and systems to ensure consistent product quality and patient safety. The Critical Aspects should be identified based on scientific product, process understanding, and system knowledge, as well as on regulatory or company quality requirements.

Since the verification activities focus on the Critical Aspects of the manufacturing system and all testing is done according to Good Engineering Practice (GEP), the new approach can lead to significant savings in capital projects. Once the Critical Aspects are identified and the core principles of the verification approach are well understood, a verification project should be easier and more cost-effective to execute than a traditional C&Q execution.

The basis of this thinking comes directly from core principles in ICH Q8 and Q9:

*ICH's Q8 Guideline on Pharmaceutical Development* gives a *scientific* basis for the Verification approach by defining core concepts for pharmaceutical product and process characterization, which focuses on the patient through Critical Quality Attributes (CQAs) of a pharmaceutical product and the related Critical Process Parameters (CPPs) that are used to control its manufacturing process.

- The evaluation of the quality risk should ultimately link back to the potential harm to the patient.

- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

The combination of these principles are core to a science- and risk-based approach and core to ASTM E2500 verification together with a number of supporting activities, such as Good Engineering Practices, design review, risk management activities, engineering change management, and the leveraging of vendor activities.

When used as intended by the E2500 standard, one can save resources without increasing the compliance risk. The verification approach encourages starting Quality Management activities much earlier in the process than the previous C&Q approach. It also encourages risk mitigation practices to design out risk, where possible, in the manufacturing system.

However, the verification approach must be combined with a set of well established Good Engineering Practices that address the fundamental quality assurance of robust and

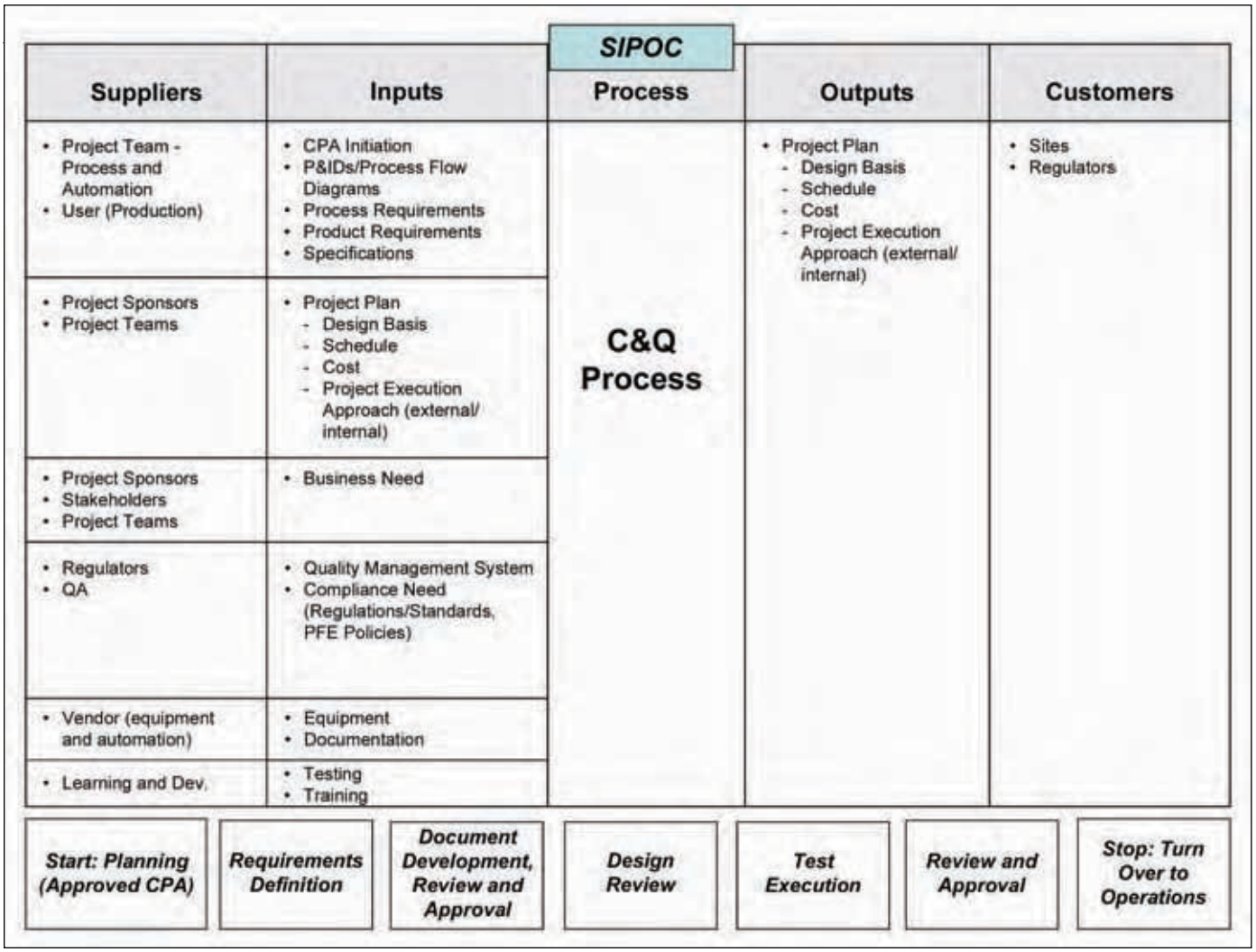


Figure 1. Pfizer Suppliers, Input, Process, Output, and Customer (SIPOC) analysis of the C&Q process.

well documented engineering, construction, and verification of a manufacturing system during its lifecycle. This includes good testing practices, good documentation practices, and an engineering change management system that can manage changes during the construction, installation, and verification phases.

## Applied Manufacturing Science

The risk assessments as well as the identification of Critical Aspects are the areas where the Quality Unit involvement is important. The Quality Unit may be involved in other activities, but at least here they must be involved. Quality also should be involved in the overall risk assessment and the verification planning. The rest of the activities should ideally be controlled by GEP, other subject matter experts, and through the leveraging of vendor test documentation.

The ASTM E2500 approach, which now has become the shared basis between the upcoming ISPE Baseline® Guide for Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment and the new GAMP® 5 guide, encourage focus on the Critical Aspects and the elimination of repetitive testing.

## Transformation to E2500 Verification

The transformation from C&Q to E2500 Verification is more than just changing practices and procedures. Within a pharmaceutical company, it requires change in roles/responsibilities, buy-in from key stakeholders, and the ability to quantify the benefit of change.

At Pfizer, our Right First Time program for continuous improvements enabled us to lead the C&Q transformation. The lean project team had colleagues from key stakeholder functions and global sites. The Pfizer lean project method includes the following stages: Define Measure, Analyze, Recommend, and Act. We developed value stream maps for the current and future state and analyzed the current issues with C&Q as mentioned above.

The final new process was reviewed against these current issues to make sure they are all addressed in the new process. Furthermore, we defined a so-called Suppliers, Input, Process, Output, and Customer (SIPOC) analysis of the C&Q process, as shown in Figure 1.

Status today is that a new Pfizer verification process has been designed based on ASTM E2500. We have completed three pilot projects on the new process at a number of Pfizer sites in parallel to developing the guidelines for the new ASTM-based process. To date, we identified average savings of 13% of C&Q costs – just through a reduction of activities and documentation. Additional streamlining opportunities in the execution of testing is being identified and assessed as part of our implementation plan. We will continue to use cost, quality, and schedule metrics to monitor the improved efficiencies of the new approach.

*Concludes on page 14.*

## Conclusion

What Pfizer, like many other companies, have experienced, is that the traditional C&Q approach is more extensive, expensive, and time consuming than necessary. The traditional approach on all direct impact systems has led to more inspection, testing, rigid change management, and other activities than necessary to achieve regulatory compliance. Most of this effort can be replaced by GEP and can be controlled by the appropriate subject matter experts who are defined within the project team.

The focus on risk to the patient and the flexible verification approach with active involvement of vendors can save resources without increasing the compliance risk. By moving much of the qualification activities to GEP, combined with good testing practices, good documentation practices, and engineering change management, significant savings can be achieved without decreasing quality or increasing regulatory risk.

We encourage companies to use the new verification approach in driving a lean approach to C&Q. Our experience to date has shown C&Q cost savings related to a reduction in documentation and test activities. Actual project savings vary depending on a site's current implementation of GEP, and application of science- and risk-based concepts in defining the manufacturing system Critical Aspects.

We are currently rolling out the new Verification approach beyond the current pilot projects and we look forward to sharing learning and experiences with other companies applying the ASTM E2500 principles. So far, it is our experience that once the concepts of the Critical Aspects are well understood, the remaining activities are a logical progression of C&Q concepts, combining Lean thinking with Good Engineering Practices and Quality Risk Management principles.

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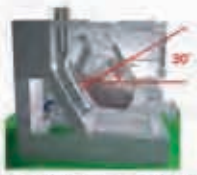


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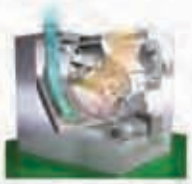

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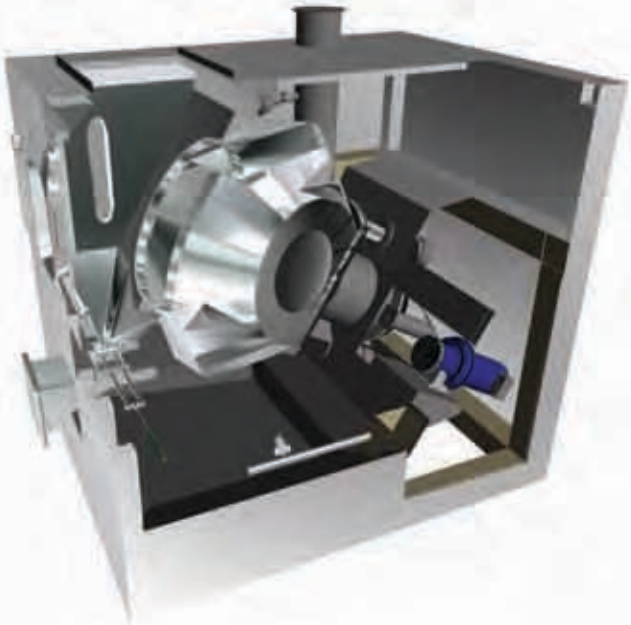

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# Case Study: Risk-Based Approach to Containment and Control for Potent/ Hazardous Compounds

by Hisao Takahashi, PE and Shigehito Nakamura

**This case study reviews an approach to containment and control and provides practical countermeasures to prevent cross-contamination from potent or hazardous compounds in pharmaceutical integrated manufacturing facilities.**

## Introduction

When both non Beta-lactam and Beta-lactam facilities are located on the same site, what kind of containment and control measures are necessary for Beta-lactam facilities to prevent cross-contamination against non Beta-lactam facilities?

Toyama Chemical Co., Ltd. has two pharmaceutical manufacturing sites, Toyama Main Campus and Toyama Second Campus[1] located in Toyama-city in Japan. In Toyama Main Campus, there are more than 10 pharmaceutical integrated manufacturing facilities dedicated to producing beta-lactam, such as penicillin and cephalosporin entities.

Toyama took on the task of separating the non beta-lactam facilities from the beta-lactam facilities, using a "Risk-Based Approach" to cross-contamination in accordance with cGMP.

## What is "Risk-Based Approach?"

After reviewing regulations and guidelines on design and construction features, chemical and physical containment controls, process operations, material and personnel flow, acceptable criteria and evaluation, Toyama paid attention to four major concerns that Toyama has to comply with:

- Operations relating to the manufacture, processing, and packaging of beta-lactam shall be performed in facilities separate from those for other products.
- Air-handling systems should be completely separated.
- Personnel and equipment from beta-lactam facility should not enter the non-beta-lactam facility.
- The separation should be qualified, procedures validated, and where necessary monitored.

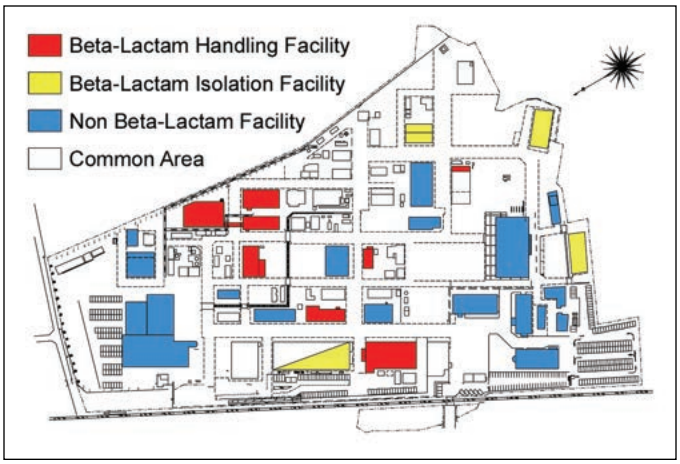


Figure 1. Layout of facility classification at Toyama Main Campus.

## Engineering and Procedural Measures

Toyama strategy's to contain the beta-lactam facilities was by focusing on appropriate engineering and procedural measures to avoid cross-contamination. The first is to design and install self-contained facilities, such as HEPA filtration system and an isolation system, the second is to organize and manage the operation and flow of personnel, materials, and products in order to avoid cross-contamination and to implement a periodic monitoring program to demonstrate no cross-contamination.

## Definition and Classification based on Beta-lactam Handling and Flows

First of all, the buildings and facilities were divided into three categories based on the level of beta-lactam exposure and handling operation - *Figure 1*. The categories were defined as follows:

### *Category 1: Beta-Lactam Facility*

The first category is the "beta-lactam facility," which handles beta-lactams, such as penicillin and cephalosporin. This category is further sub-divided into two classifications, depending on the handling systems used and the risk of beta-lactam exposure.

- ***Beta-Lactam Handling Facility***

The first is a "beta-lactam handling facility," which means that beta-lactam raw materials, intermediates, or products are not handled in a closed system (such as an isolator) in relation to the manufacturing and processing in the facility.

- ***Beta-Lactam Isolation Facility***

The second is the "beta-lactam isolation facility," which means that beta-lactam raw materials, intermediates, or products are handled in a closed system by using containment and/or an isolator system. In addition, packaged drug products are stored in a warehouse and liquid beta-lactam materials, such as a waste, has little exposure risk.

### *Category 2: Non Beta-Lactam Facility*

The second category is a "non beta-lactam facility/building" that has not handled beta-lactams. There are no cross-personnel and materials between non beta-lactam and beta-lactam facilities. In addition, air-handling systems are completely separate from beta-lactam facilities.

### *Category 3: Common Area*

The third category is the "common area" that has not handled beta-lactams. However, there is possible cross-contamination between individuals in non beta-lactam facilities and individuals in beta-lactam facilities. For example, in the cafeteria, administration office, or on the streets of the campus.

Figure 1 shows Toyama's Main Campus layout and facility classification based on the definitions. There are several beta-lactam handling facilities in red and beta-lactam isolation facilities in yellow.

Toyama referred to the Control of Substances Hazardous to Health (COSHH) essentials[2] within red line and modified and extended it in Table A since the handling conditions are different in each area or operation. Exposure Predictor Solid (EPS) is divided based on handling mass and dustiness of materials. For example, if an amount of handling mass is small mg size and material's state is wet cake or solution, the exposure solid band is defined as EPS-1. The big difference from COSHH is the expansion of the band. EPS-G and EPS-C are added to EPS-1 to EPS-4. EPS-G is next to EPS-1. EPS-G acts as a barrier between the beta-lactam exposure environment and the clean environment. Therefore, "G" means "Guard area." There is, of course, no handling of beta-lactam in EPS-G. EPS-C is an outside area next to EPS-G and it has no potential contamination of beta-lactams. Therefore, "C" means "Clean area." Toyama defines EPS-1 to EPS-4 as the "Beta-lactam Exposure Area," and defines EPS-G and EPS-C as the "Beta-lactam Free Area," respectively.

## Acceptance Criteria of Beta-Lactam Containment and Control

Table B shows the categories of physiological activity based on inherent properties, such as, Occupational Exposure Limit (OEL), Acceptable Daily Intake (ADI), Swab Limit, and Short-Term Exposure Limit (STEL). The table is based on various laws and regulations relating to Environment, Health, and Safety (EHS) in the US and Europe.[3,4]

Which category is an appropriate level for the containment of beta-lactams?

| Dustiness \ Handling Mass | | No (Next to EPS-G) | No (Next to EPS-1) | Small (mg) | Middle (kg) | Large (ton) |
|---|---|---|---|---|---|---|
| No | In a Vessel, Bottle | EPS-C | EPS-G | Not Applicable | Not Applicable | Not Applicable |
| Low | Wet Cake, Liquid, Tablet, Capsule, etc. | | | EPS-1 | EPS-1 | EPS-2 |
| Mid | Granule, Vessel/Cloth-attached, etc. | | | EPS-1 | EPS-2 | EPS-3 |
| High | Fine particle, Powder, Small Grain, etc. | | | EPS-2 | EPS-3 | EPS-4 |

Table A. Exposure predictor solid band.

| Property \ Category | | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| OEL (8 hr shift) | $\mu g/m^3$ | > 1,000 | 100 – 1,000 | 10 – 100 | 1 – 10 | 0.1 – 1 | < 0.1 |
| ADI | $\mu g/kg \cdot d$ | > 100,000 | 1,000 – 100,000 | 100 – 1,000 | 10 – 100 | 1 – 10 | < 1 |
| Swab Limit | $\mu g/100\ cm^2$ | > 100,000 | 1,000 – 100,000 | 100 – 1,000 | 10 – 100 | 1 – 10 | < 1 |
| STEL < 3*OEL (15 min) | $\mu g/m^3$ | > 3,000 | 300 – 3,000 | 30 – 300 | 3 – 30 | 0.3 – 3 | < 0.3 |
| OEL : Occupational Exposure Limit | | ADI : Acceptable Daily Intake | | STEL : Short-Term Exposure Limit | | | |

Table B. Exposure tolerance category.

| Object | Exposure Tolerance ADI Conversion |
|---|---|
| Beta-Lactam Handling Facility Exhaust Air | 0.72 μg/kg·day |
| Non Beta-Lactam Facility Supply Air | 0.0072 μg/kg·day |
| Assumption for Calculation<br>• Average Weight of Japanese : 53.3 kg[6, 7, 8]<br>• Average Breath Frequency : 16 times a minute[9]<br>• Respiratory Volume : 500 mL a time[9]<br>• Exposure Time : 8 hours a day | |
| Calculation Formula<br>$\frac{\text{Exposure Tolerance } (\mu g/m^3) \times 500 * 10^{-6} \text{ (m}^3\text{/time)} \times 16 * 60 \text{ (time/hr)} \times 8 \text{ (hr/day)}}{53.3 \text{ (kg)}}$ | |

Table C. ADI consideration.

Toyama investigated whether beta-lactam acceptance criteria, such as an airborne limit and swab limit on the surface, have been set in a beta-lactam facility and/or a non beta-lactam facility. Unfortunately, there was not an appropriate acceptance criteria. Therefore, Toyama established the acceptance criteria based on risk assessment.

According to COSHH, the strictest standard of the OEL is 10 μg/m$^3$ (except for carcinogenic or genotoxic compounds or except for some genotoxic compounds).[2] And, according to the FDA, potent compounds have biological activity of less than 15 μg/kg or daily dose of less than 1 mg and OEL less than 10 μg/m$^3$.[5] As a result, Toyama decided to set the acceptable level of beta-lactam containment in compliance with the COSHH and FDA regulations and guidelines. Furthermore, Toyama considered cleaning validation criteria. The OEL of highly active substance is less than 10 μg/m$^3$ according to COSHH and FDA regulations. This level is classified into Category 4 on Table B. Moreover, a criterion of cleaning validation is generally 400 μg/100 cm$^2$ by the visual observation method. This level is in Category 3. Therefore, Toyama set Category 4 as the acceptable level of beta-lactam containment.

### *Exposure Tolerance*

- ***Beta-Lactam Handling Facility***
  - Airborne Limit of Exhaust Air - < 10 μg/m$^3$
  - Swab Limit on the Entrance - < 1 μg/cm$^2$ (100 μg/100 cm$^2$)
- ***Non Beta-Lactam Facility***
  - Airborne Limit of Supply Air - Not detect (Detection Limit; 0.10 μg/m$^3$)*
  - Swab Limit on the Entrance - Not detect (Detection Limit; 0.0003 μg/cm$^2$)*

*In the case of Piperacillin, a penicillin antibiotic.

The ADI consideration is important for potent and hazardous compounds. The amount of beta-lactam was calculated when the worker took the exposure tolerance quantity all day long. This result is shown in Table C as an ADI conversion value.

The calculation result is less than 1 μg/kg day of an exhaust air from a beta-lactam facility and less than 0.01 μg/kg day in non beta-lactam facility and it corresponds to Category 6 in the previous control bands.

## Approach to Beta-Lactam Containment Methodology

Table D shows what kind of engineering approach is suitable to control each airborne limit. This table refers to COSHH essentials with modifications by Toyama.[2] EC1 is a general ventilation system and EC4 is a strict containment system, such as an isolator system. The containment system should be selected for each area (EPS) based on the containment performance of the engineering controls and readiness of system operation.

As previously mentioned, exposure tolerance of beta-lactams was set to 10 μg/m$^3$. Therefore, it is necessary to install each system that applies to the highlighted area in red to meet acceptable criteria.

### *Actual Countermeasure*

- EPS-C - Install a middle efficiency grade filter (ASHRAE[10,11] > 80) in the exhaust system. Prepare an airlock in a facility where it had not been set.
- EPS-G - Install a high efficiency grade filter (ASHRAE 98) in the exhaust system.
- EPS-1 - Install a high efficiency grade filter (ASHRAE 98) in the exhaust system.
- EPS-2 - Install a high efficiency grade filter (ASHRAE 98) in the exhaust system.
- EPS-3 - Install a HEPA filtration system in the exhaust system. Install a dust collection system for process equipment.
- EPS-4 - There is no applicable area at Toyama Main Campus.

| EPS Classification / Containment System | | | Airborne Limits μg/m$^3$) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | EPS-C | EPS-G | EPS-1 | EPS-2 | EPS-3 | EPS-4 |
| EC1 | General Ventilation | Ventilation | < 1 | 1 – 10 | 10 – 100 | 100 – 1,000 | 1,000 – 10,000 | > 10,000 |
| EC2 | Flow Control | Local Exhaust | < 1 | < 1 | 1 – 10 | 1 – 100 | 100 – 1,000 | 1,000 – 10,000 |
| EC3 | Containment | HEPA Filtration Draft Chamber | < 1 | < 1 | < 1 | < 1 | 1 – 100 | 10 – 100 |
| EC4 | Strict Containment | Isolator Bag-In/Bag-Out | < 1 | < 1 | < 1 | < 1 | < 1 | < 1 |

Table D. Classification of containment performance.

## The Preliminary Study on Beta-Lactam Exposure

Toyama planned a preliminary study to take precautionary measures against cross-contamination of beta-lactams more effectively. The objective of this study was to evaluate the impact of the cross-contamination from beta-lactam exposure. Toyama prepared a test facility that simulated the three beta-lactam exposure levels (EPS-1, EPS-G, and EPS-C), and evaluated the impact of the cross-contamination - *Figure 2*. The ceiling and walls are made of gypsum board finished with PolyVinyl Chloride (PVC) resin enamel paint and the floor is covered with sheets of PVC - *Figure 3*. In addition, this facility contains an air circulation system with a filter unit to simulate certain beta-lactam exposure levels, similar to an actual manufacturing facility - *Figure 4*. The rate of air circulation was 8.5 times/hr.

Toyama simulated the environmental conditions of EPS-1, EPS-G, and EPS-C levels inside the test facility by spraying "Piperacillin," a penicillin antibiotic. The model environmental condition at each area was set to EC1 line in Table D. This value was converted into a swab limit value in Table B, and it was defined as the expected level in this study. The expected and actual exposure level of beta-lactam at each area is shown in Table E. The test was able to create the environmental condition almost equal to the expected level.

Figure 2. External view of test facility.

Figure 3. Interior of test facility.

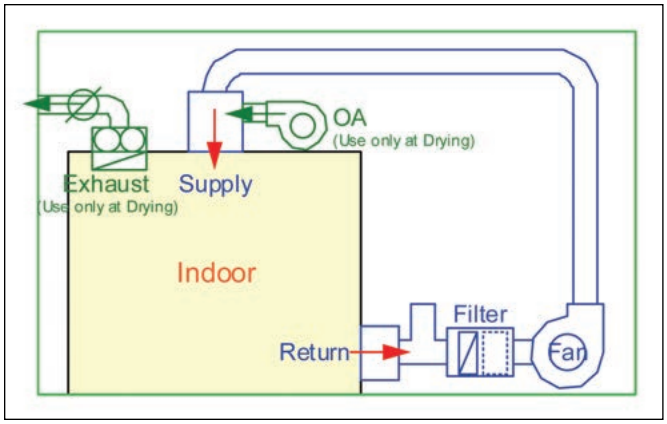


Figure 4. Air circulation system of test facility.

| Exposure Level | Beta-Lactam Swab Limits (Av. of Ceiling, Wall, Floor) ($\mu g/cm^2$) | |
|---|---|---|
| | Expected Level | Actual Measurement |
| EPS-1 | 10 | 16.4 |
| EPS-G | 1 | 1.2 |
| EPS-C | 0.1 | 0.06 |

Table E. Simulated environmental condition.

The surface density of Piperacillin on six inner walls could be contaminated almost uniformly and this substance was not decomposed for test period (8 hrs) - *Figure 5*.

This study generated some interesting results.

### *Result 1: Contamination on the Clothing*

The first test evaluated the amount of beta-lactam contamination on the clothing. The clothing was exposed to test environmental conditions for some determined duration. In all of test levels, beta-lactams were not detected on the clothing - *Table F*. The potential of contamination to clothing seems to be lower at these exposure levels.

This result leads to the conclusion that there is less possibility of beta-lactam contamination that could spread from the cloth for working at the beta-lactam free area. At Toyama, all operators have their own clothing and change when going into or out of the beta-lactam handling facilities.

### *Result 2: Contamination by Walking*

The second test evaluated the amount of beta-lactam contamination spread by walking. A number of plastic tiles set on the road were trod by shoes that walked 150 walking steps inside the test room. Figure 6 shows a possibility of beta-lactam contamination expansion by walking. Some very interesting results came out from this study. The beta-lactam density on the surface of plastic tile set on the road tentatively trod by the first step was about one percent of the beta-lactam density on the floor of test room in each test. Naturally, the beta-lactam density on the tiles gradually decreases with walking distance. However, beta-lactams are detected on the tiles even if after walking 200 meters except on EPS-C.

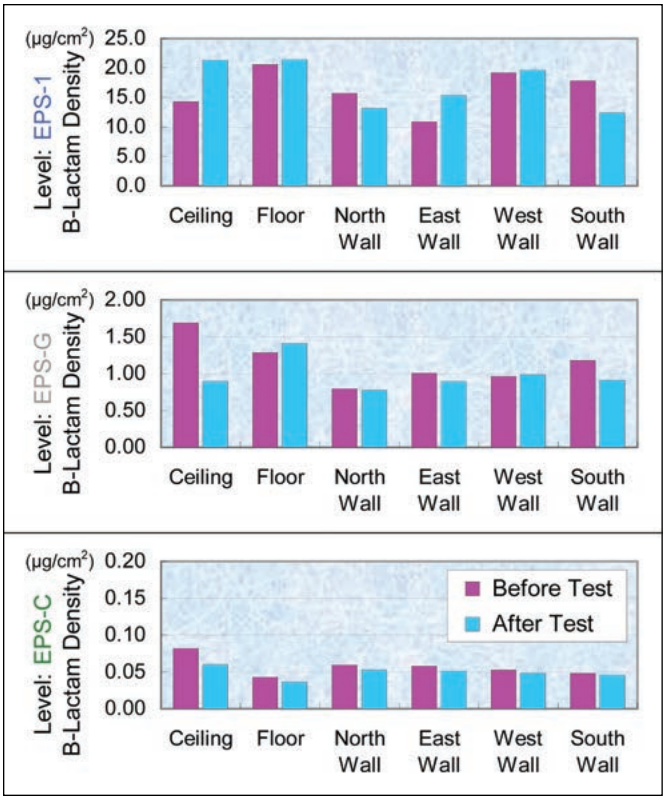


Figure 5. Beta-lactam surface density inside the test facility.

This result leads to the conclusion that there is a possibility of beta-lactams diffusion from shoes up to 200 meters distance. At Toyama, all operators put on their own shoes in beta-lactam handling facilities and change when leaving the facilities.

### *Result 3: Effect of Decontamination*

The third test evaluated the effect of cleaning agent for beta-lactam decontamination. The shoes that walked 150 walking steps inside the test room were soaked in cleaning agent for 10 seconds. The shoe sole was definitely contaminated by beta-lactams in each test environmental condition, including on EPS-C and it is possible to decontaminate by the cleaning agent for 10 seconds as shown in - *Figure 7*.

This result leads to the conclusion that even if the shoes are contaminated with beta-lactams, they can be decontaminated with the cleaning agent. At Toyama, all operators decontaminate their shoes at airlock when they go out of beta-lactam handling facilities as a precautionary measure of cross-contamination.

| Exposure Level | Beta-Lactam Density (μg/cm²) Operation | | | | | |
|---|---|---|---|---|---|---|
| | 2 hrs | 4 hrs | 6 hrs | 8 hrs | 48 hrs | 90 hrs |
| EPS-1 | N.D. | N.D. | N.D. | N.D. | N.D. | N.D. |
| EPS-G | N.D. | N.D. | N.D. | N.D. | | |
| EPS-C | N.D. | N.D. | N.D. | N.D. | | N.D. |
| N.D. : Not Detected | Detection limit : 0.0009 μg/cm² | | | | | |

Table F. Contamination on the clothing.

## Operations and Flows of Personnel, Materials, and Products

Toyama prepared Standard Operating Procedures (SOPs) for operations and flow of personnel, materials, and products for the beta-lactam cross-contamination prevention in accordance with the preliminary study result, each regulation, and guideline.[12-22] The SOPs provide all measures to prevent cross-contamination of beta-lactams from an ordinary activity to extraordinary action, such as disaster prevention training. Personnel flows and document flows and some operational rules are described in the following as an example.

### *Personnel Flows*

The SOPs provide the following rules for personnel flows:

- The person who leaves the beta-lactam exposure area should change clothes, wash one's hands, and change shoes.
- The person who entered the beta-lactam exposure area cannot enter the non beta-lactam facilities on the same day. If the person hopes to enter the non beta-lactam facility in case of emergency, such as an accident, they should take a bath or shower and change clothes.
- The person who leaves the beta-lactam handling facility should go out via EPS-C, and must not go out directly from EPS-G and the beta-lactam exposure area.
- If an individual is to enter both the beta-lactam and the non beta-lactam facilities on the same day, they should first enter the non beta-lactam facility and then the beta-lactam facility to prevent cross contamination inside the non beta-lactam facility.

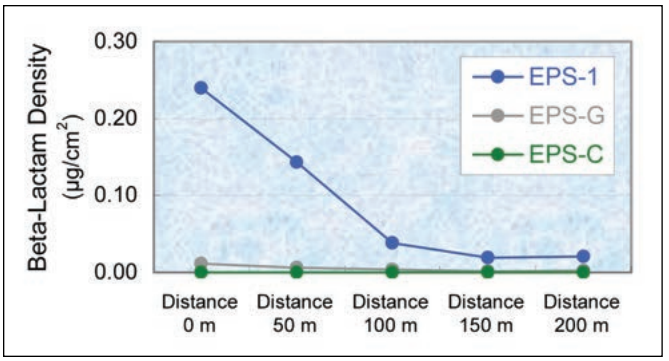


Figure 6. Contamination by walking.

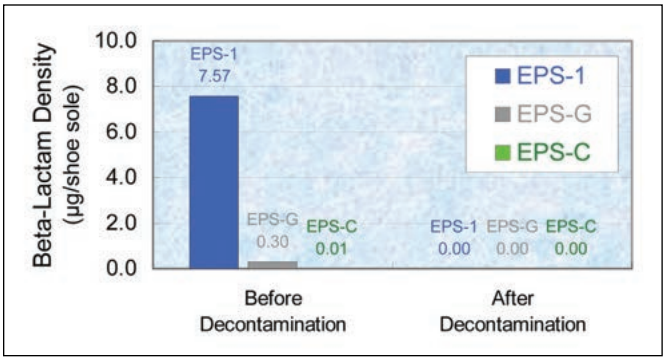


Figure 7. Effect of decontamination.

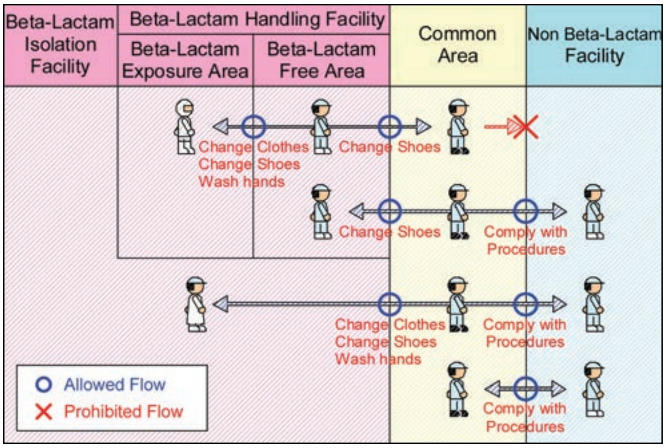


Figure 8. Rules of personnel flow.

Figure 8 shows which personnel flow is allowed and which one is prohibited.

### *Document Flows*

The SOPs provide the following rules for document flows:

- The document written in the beta-lactam facility, including the beta-lactam isolation facility, should not be brought into non beta-lactam facility.
- The document should be opened only in the dedicated room inside the beta-lactam facility for its review and storage.
- The document written in the beta-lactam exposure area should be sealed up with a clean case or bag when it is brought out from facility.
- The document sealed up should be opened only in the dedicated room for its review and storage.

Figure 9 shows which document flow is allowed and which one is prohibited.

### *Typical Operation Rules*

- The product or material brought out of the beta-lactam exposure area should be enclosed in a container or bag and sealed up.
- Beta-lactams should be loaded on the track only for transportation of beta- lactams.

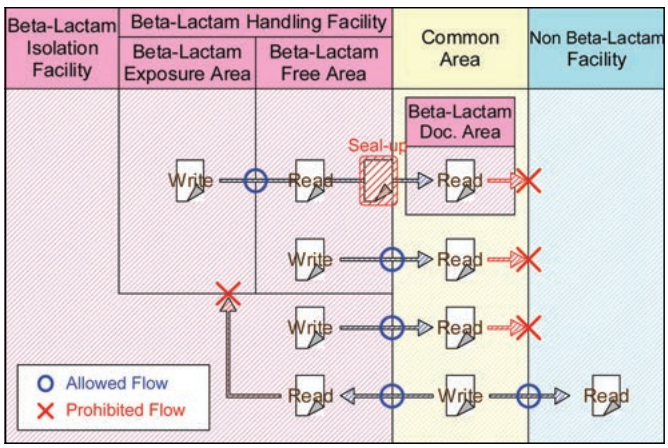


Figure 9. Rules of document flow.

| Exposure Level | Room/Area | Handling Mass<br>Handling Material |
|---|---|---|
| EPS-4 | Not applicable | |
| EPS-3 | Weighing Room | Several kilograms<br>Fine particle |
| EPS-2 | Air-Shower Room | Small mass<br>Powder attached to cloth |
| EPS-1 | Changing Room | Extremely small mass<br>Powder attached to cloth |
| EPS-G | Air-Lock | |
| EPS-C | Hall | |

Table G. Handling situation of beta-lactam at monitor facility.

- The tool and the measurement instrument used for maintenance and/or calibration should be prepared for the beta-lactam facility use only.
- The waste brought out from the beta-lactam exposure area should be enclosed in a container or bag and be sealed up. The sealed up container should be sent to a dedicated space without opening until being carried away from the campus.

## Beta-Lactam Density Investigative Study

Toyama planned a verification study in order to investigate the actual condition of beta-lactam contamination at the beta-lactam handling facility after the prevention measures of beta-lactam cross-contamination had been executed. The penicillin product manufacturing facility was selected as a monitor facility. The monitor substance is "Piperacillin" and the monitoring methods are air sampling and swab sampling at each exposure area. Table G shows the handling situation of beta-lactams at the monitoring facility.

Figure 10 shows the beta-lactam density in air sample at each area. In the condition of at-rest, beta-lactam density in all areas did not exceed the acceptable criteria of 10 µg/m$^3$. However, beta-lactam density exceeded the acceptable criteria in EPS-3 and EPS-2 in-operation condition. These results prove clearly that EPS-G and EPS-C were not contaminated with beta-lactams in spite of a large amount of beta-lactam exposure in EPS-3 and EPS-2.

Figure 11 shows beta-lactam contamination condition on the floor in each area. These results prove that EPS-G and EPS-C were not contaminated with beta-lactams as with results in Figure 10.

Figure 12 shows accumulation on the wall of beta-lactams for a week. In this facility, the floor is cleaned every day and the wall is cleaned every weekend. The accumulative amount of beta-lactams for five days was less than 1 µg/cm$^2$ (exposure tolerance of swab) though the amount of it attached to the wall was increased day by day.

From these results, in EPS-3 and EPS-2, the detected beta-lactams were more than within the acceptable limit. However, beta-lactams were not detected in beta-lactam free area, such as EPS-C and EPS-G. In conclusion, Toyama's program is effectively containing beta-lactams.

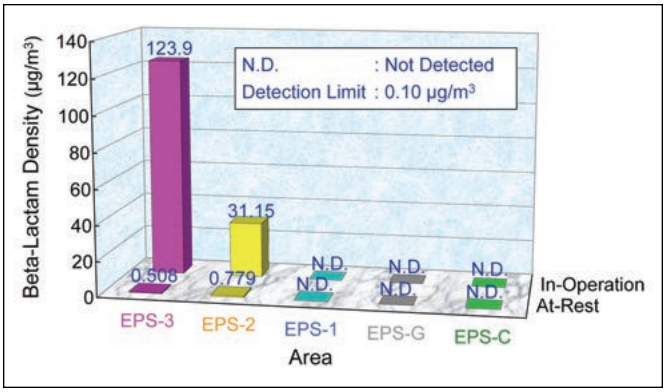


Figure 10. Beta-lactam density in air.

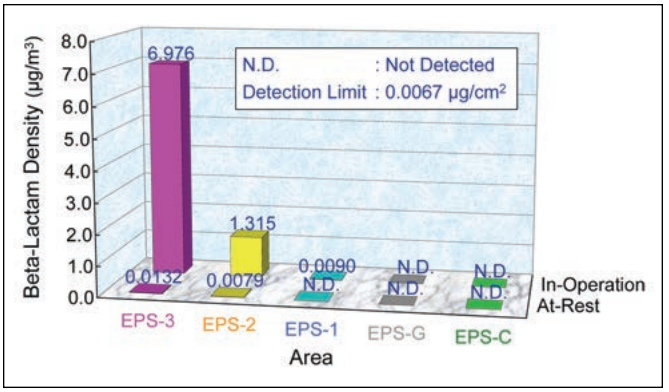


Figure 11. Beta-lactam density on floor.

## Long-Term Monitoring Program of Beta-Lactam

Toyama planned a long-term monitoring program in both the beta-lactam facilities and non beta-lactam facilities to evaluate the appropriateness of their beta-lactam containment methodology. The monitoring program was designed to take samples of exhaust air and swab samples on the floor in high traffic zones at the beta-lactam facilities and to take samples of inlet air and swab samples on the entrance floor at non beta-lactam facilities. The monitoring schedule is preplanned at 0, 1, 2, 3, 6, 9, 12, 18, and 24 months, and from then onward every 12 months. In addition, in the case of unscheduled events, such as remodeling of the facility or removing of beta-lactam equipment, the monitoring program should be conducted irregularly.

Toyama has already finished the monitoring for initial 18 months (eight times) as of June 2009. Beta-lactams were within the acceptable limit in all of facilities at any time. The containment and control program for cross-contamination prevention of beta-lactams of Toyama has been successful at this time. However, Toyama has to continue this program until it discontinues manufacturing and handling of beta-lactams.

## Conclusion

Toyama has established an appropriate engineering approach and operational management for containment/separation of beta-lactams based on scientific rationale and preliminary study results. The containment and control program of Toyama has been successful and qualified by periodic monitoring.

In recent years, the trend in the drug development has been toward the discovery research of substances that have effect at lower dose. These high potency substances and hazardous materials, such as steroids, hormones, or anti-cancer agents, should be isolated from manufacturing operation for other products. It is considered that a high potency substance will be manufactured in a pharmaceutical facility where there are lots of pharmaceutical integrated manufacturing facilities in one site.

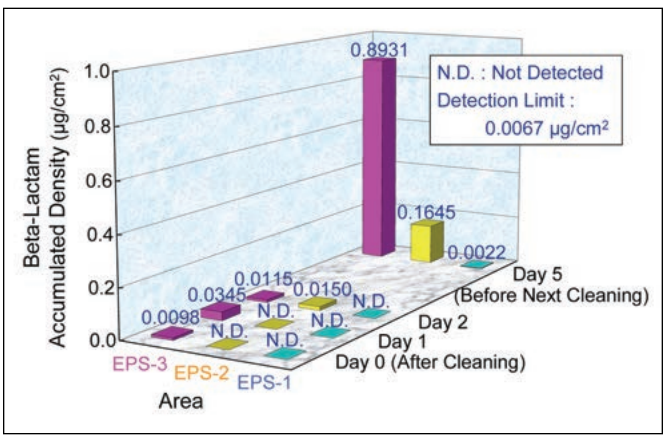


Figure 12. Accumulation of beta-lactam on wall.

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## Latin America

### *Argentina*

*Manufacturing License for Medicinal Products*[1]

The National Administration of Food, Drug, and Medical Technology (ANMAT) released on September 2009, instructions listing all the documents required for a manufacturing license application for medicinal products. These instructions also provide information for a modification of a manufacturing site, including a variation of the manufacturing license.

These instructions list the relevant guidelines to be complied with according to the type of product manufactured.

## Europe

### *Poland*

*GMP Inspection*[2]

On 31 July 2009, the following model of documents was provided along with the new Decree 09.129.1069 on the Control and Inspection Conducted by State Pharmaceutical Inspection and for Conclusions Regarding Quality of the Samples. The following forms were made available: Annex 1: Authorization for Pharmaceutical Inspector to Effectuate a Control; Annex 2: Authorization for Inspector of Manufacturing Matters of the Main Pharmaceutical Inspectorate to conduct an inspection; Annex 3: Protocol Confirming that Samples Have Been Taken; Annex 4: Conclusions Regarding the Result of Quality Examination of the Samples Taken During the Control or Inspection and Annex 5: Book of the Control.

This Decree replaces the previous one dated 15 October 2008.

### *Russia*

*Medicines Manufacturing Licensing*[3]

By this new amendment made on 8 August 2009 to the Decree N 415 (dated 6 July 2006), the Ministry of Health released a regulation on the process of medicines manufacture licensing (requirements to license, application, and license granting procedures).

This Decree replaces the previous Decree N 415 of 6 July 2006 on the Approval of Manufacturing Licenses for Medicinal Products, as last amended on 19 July 2007 and came into force on 14 August 2009.

### *United Kingdom*

*GMP*[4]

The Medicines and Healthcare products Regulatory Agency (MHRA) published on 24 August 2009 guidance on the introduction of a new risk-based inspection program applied by the MHRA for GMP Quality Control Laboratories.

This program is part of a risk-based inspection process implemented on 1 April 2009 and aims to minimize the burden on the regulated industry while maintaining the required levels of public safety.

### *EDQM*

*Revised Procedures for Submitting Applications*[5]

The European Directorate for the Quality of Medicines and Healthcare (EDQM) has adopted a revised procedure that companies will have to follow when submitting applications for certificates of suitability (CEPs), which guarantee that the quality of a company's pharmaceutical substances comply with the relevant monographs of the European Pharmacopoeia.

The revised procedure that came into force on the 1 September 2009 introduced new requirements for electronic and paper submissions for CEP applications.

CEPs are recognized by all signatory states of the European Pharmacopoeia Convention and by the European Union. There are also other countries that have chosen to recognize them. Where the active substance and/or raw and starting material or excipients are the subject of a monograph of the European Pharmacopoeia, the CEP can be used by the manufacturer of a medicinal product in its application for a marketing authorization to demonstrate the substance's compliance with the European Pharmacopoeia.

There are three possible formats for electronic submissions, but the EDQM recommends using the eCTD format.

With these revised procedures, an e-submission for a request for revision will be permitted even if the original documentation was not submitted electronically. However, once an e-submission is sent, all future data related to the application would have to be submitted in electronic format to be compliant with the new requirements in order to avoid the rejection of the submission.

### *EMEA Updates*

*EudraGMP*[6]

The European database on pharmaceutical manufacturing and import authorizations, EudraGMP, has been made publicly accessible by the European Medicines Agency (EMEA) beginning August 2009.

The version of the database that has been opened to the public is an update of the EudraGMP 2.0 database created in April 2007 with the goal of facilitating the exchange of information on compliance with GMP between the European Regulatory Competent Authorities network (i.e., EU member states, Iceland, Liechtenstein, and Norway).

The database covers both human and veterinary medicinal products and with this new version, information about manufacturing, importation authorizations, and GMP certificates will be now available to the public.

The agency expects that by January 2011 the public will have access to data from all national competent authorities.

## Asia

### *India*

*Defective Products*[7]

The Central Drugs Standard Control Organization (CDSCO) published guidelines to harmonize implementation of the Drugs and Cosmetics Act and Rules in order to fight against the manufacture of counterfeit and adulterated drugs. Three different categories for quality defects are defined and referenced in these guidelines: Category A: spurious and adulterated drugs; Category B: grossly sub-standard drugs; Category C: minor defects.

### *Philippines*

*Annual Reports of Marketing Expenditures*[8]

On 21 September 2009, a proposed

law in the Philippines was introduced in order to require pharmaceutical companies to submit annual reports of their marketing expenditures to the health secretary.

The House Bill 6418, or the Annual Marketing Expenses Report for Drug Manufacturers Act of 2009, seeks to create policy decisions on the problem of high medicine costs. Representative Diosdado Arroyo, author of the bill, expressed his concerns that some medicines sold by multinational drug companies in the Philippines are priced higher than in other countries (like India and Pakistan).

This proposed law would authorize the health secretary to require prescription drug manufacturers/labelers to submit reports on the marketing costs of each drug dispensed in the country.

## International

### *GMP*[9]

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) released on 1 September 2009 a new guide to GMP for Medicinal Products and its Annexes, replacing the previous one dated 12 November 2008. This guide aims to avoid barriers to trade in medicinal products, to promote uniformity in licensing decisions, and to ensure the maintenance of high standards of quality assurance in the development, manufacture, and control of medicinal products.

There are two parts of this guide: Part I includes GMP principles for the manufacture of medicinal products, while Part II covers GMP for active substances used as starting materials.

## Australia

### *Manufacturing Principles for Medicinal Products*[10]

At the end of July 2009, the Therapeutic Goods Administration (TGA) National Manager determined new principles to be observed for manufacturers of medicinal products (including active pharmaceutical ingredients and sunscreen products). This new updated Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2009 has been released in order to bring Australian manufacturing requirements into line with current international practices by adopting the Guide to GMP for Medicinal Products issued by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) in January 2009.

The main changes are related to product quality reviews and sterility requirements as the product quality reviews will involve periodic assessment of past reviews, in-process controls, failed batches, deviations and nonconformities, process or equipment changes, marketing authorization variations, stability results, complaints and recalls, and technical agreements to identify improvements.

Annex 1 of the new principles is related to the manufacture of sterile medicinal products and reflects changes to particle count limits, airflow monitoring in Grade A processing areas, protective clothing requirements, limits to aseptic process media fills, and capping and crimping aseptically filled vials.

## Canada

### *Safety Update on TNF Blockers and Risk of Cancer in Children and Young Adults*[11]

Health Canada announced on 20 August 2009 to healthcare professionals and Canadians working with manufacturers that they will further strengthen product labeling for Tumor Necrosis Factor (TNF) blockers to reflect the increase risk of cancer in children and young adults. TNF blockers are used to treat patients with chronic inflammatory diseases, including Juvenile Idiopathic Arthritis (JIA), rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ankylosing spondylitis (a type of arthritis).

Five TNF blockers are currently authorized in Canada: Enbrel (etanercept), Remicade (infliximab), Humira (adalimumab), Simponi (golimumab), and Cimzia (certolizumab pegol).

Health Canada already communicated in the past the risk of the development of certain types of cancers, including lymphoma, associated with the use of these drugs.

### *GMP Guidelines Drugs used in Clinical Trials*[12]

This Annex 13 to the current edition of the Canadian "Good Manufacturing Practices Guidelines" (GUI-0001) has been released by Health Canada and is intended to provide guidance relevant to the manufacture and packaging/labeling of drugs intended for use in human clinical trials, including the placebo and comparator product.

The Health Products and Food Branch Inspectorate (the Inspectorate) has based this Annex on the current Pharmaceutical Inspection Cooperation Scheme's (PIC/S) version of their Annex 13 "Manufacture of Investigational Medicinal Products" (IDRAC 39695) with changes necessary to adapt the text to meet Canadian requirements.

This guideline will come into force on 1 December 2009 and replaces the previous version of the GMP guidelines named "Manufacture of Drugs Used in Clinical Trials" dated 1 April 2004.

### *GMP: Program Review*[13]

Health Canada is currently conducting a review of its GMP inspection program for drug establishments in an effort to make the program more risk-based.

This GMP Review Consultation can be completed on-line and the consultation workbook available on the Health Canada Web site. Stakeholders are encouraged to participate in this GMP Review Consultation as their input will be critical on how the risk of an establishment is assessed; on appropriate inspection cycles for different levels of risk; and on tools that can be developed to make the inspection program more risk focused.

The online workbook can be completed and submitted starting 15 September 2009 until 30 November 2009 inclusive.

### *Common Drug Review*[14]

The Common Drug Review Submission (CDR) Guidelines for Manufacturers were released by the Canadian Agency for Drugs and Technologies in Health (CADTH) at the end of July 2009, providing guidance to manufacturers in the preparation of submissions for new drugs, submissions for new combination

products, submissions for drugs with new indications, submissions for pre-NOC drugs, and for resubmissions. The submissions and resubmissions must meet the needs of the CDR Directorate and participating federal/provincial/territorial (F/P/T) Drug Plans.

### *GMP Compliance of Foreign Sites*[15]

Health Canada published guidelines regarding the type of information that should be submitted to the Health Product and Food Branch Inspectorate in order to assess the compliance of foreign sites with the Canadian GMP regulations.

Outcome of the assessment by the Inspectorate will be a Compliant (C) or Non Compliant (NC) rating for the foreign site or a request to submit additional information.

Forms also are included in this guideline, such as Foreign Site Submission Form, Request for an Inspection of a Foreign Site Form, Foreign Site Inspection Services Agreement Form, and Audit Report Form.

This document replaces POL-0013 "Conditions for Acceptance of Foreign Inspection Reports for Listing Foreign Sites on Canadian Establishment Licenses" and was published on 1 August 2009.

## *Canada Draft Guidelines Open for Consultation*

Following issues brought to the attention of the Inspectorate, Health Canada published several revised guidance documents (listed below) that were open for consultation from 7 August 2009 to 5 November 2009.

### *Alternate Sample Retention Site*[16]

The guidance on Inspectorate's quality management process named "Alternate Sample Retention Site Guidance" (GUI-0014) has been reviewed and are intended for distributors and importers of pharmaceutical, radiopharmaceutical, biological, and veterinary drugs intending to store retention samples outside of Canada.

By releasing these draft guidelines, Health Canada wants to facilitate compliance to Section C.02.025 of the Food and Drug Regulations and to enhance consistency in the application of the regulatory requirements by describing the requirements regarding alternate sample retention sites for finished drug products. Main changes include revisions to the scope section, the appendix section, and removal of the list of non-prescription drugs.

### *Draft Guidelines: Temperature Control of Drug Products during Storage and Transportation*[17]

The draft guidance on Inspectorate's quality management process named "Temperature Control of Drug Products during Storage and Transportation" (GUI-0069) has been reviewed and was published by Health Canada on 4 August 2009.

The main changes include additional requirements to the Warehousing and Storage, Product Transportation and Products in Transit, Receiving and Documentation sections; and examples in the Interpretation sections for context.

### *Classification of GMP Observations*[18]

Health Canada released this draft guideline on the Risk Classification of GMP Observations revising the previous version. The purpose of this draft is to classify the observations noted during establishment inspections according to their risk, to ensure uniformity among the inspectors of the Health Products and Food Branch Inspectorate in the attribution of the rating following establishment inspections, to inform the industry of the situations that the Inspectorate considers unacceptable and that will generate a Non-Compliant (NC) rating following an inspection.

### *GMP: Schedule D Drugs*[19]

Health Canada has provided the revision of the following Annex 2 for the Good Manufacturing Practices for Schedule D Drugs Part 1, Biological Drugs (including Fractionated Blood Products), dated from 30 June 1999.

The main changes to the guideline are the following: interpretations were added and renumbered to correspond with changes to GMP Guidelines, 2009 edition. The interpretation of GMP requirements for the collection and processing of human blood and blood components are not within the scope of this guidance.

## *United States*

### *Guidance for Industry: Pharmaceutical Components at Risk for Melamine Contamination*[20]

On 7 August 2009, the Food and Drug Administration (FDA) made available the following guidance for the industry "Pharmaceutical Components at Risk for Melamine Contamination." This particular guidance is intended for manufacturers as it provides recommendations that will help pharmaceutical manufacturers of finished products, repackers, other suppliers, and to pharmacists who engage in drug compounding to 0avoid the use of components that are at risk for melamine contamination.

### *Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products*[21]

The draft guidance on Clinical Studies of Allogeneic Pancreatic Islet Cell Products for the treatment of Type 1 diabetes mellitus released by the FDA in May 2008 has been finalized. The FDA published the final version on 17 September 2009 of this guidance intended in order to help manufacturers, sponsors, and clinical investigators by identifying data and information obtained during Investigational New Drug (IND) studies that might be helpful in establishing the safety, purity, and potency of a biological product.

## *South Africa*

### *Guidance for Industry: Regarding Submission of the Screening Copy of an Application for Registration*[22]

On 11 August 2009, the Medicines Control Council of South-Africa (MCCZA) published a guideline for manufacturers providing information on documents required when sending applications in order to register a medicine.

Details in this guidance are provided

on dossier structure as well as on how to submit the dossier to the MCCZA. This guideline aims at making sure applications are complete to avoid delays during the screening and review process from the MCCZA.

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# PQLI Update from Strasbourg

By Dr. Kate McCormick, ISPE European Education Advisor

Industry representatives and senior regulators attending the PQLI seminar in Strasbourg heard latest developments in ICH Q8(R1), Q9 and Q10 implementation.

Susanne Keitel of EDQM sounded a note of caution. QbD is an optional approach and companies may not wish to adopt it for their whole portfolio. A tiered system is therefore needed. Keitel confirmed that flexibility is already written into the European Pharmacopoeia and explained the new non-mandatory sections on FRCs had been added to monographs for information only. In conclusion, Keitel emphasised that whatever approach to development is chosen, safeguarding public health should be the first priority.

# ISPE Strasbourg Conference a Success

Pharmaceutical science and manufacturing industry professionals from around the world gathered in Strasbourg, France to share expertise and gain insight to "Managing Knowledge through Science and Risk Assessment" at the 2009 ISPE Strasbourg Conference.

500 industry specialists from manufacturing companies, suppliers, and regulatory agencies gathered 28 September through 1 October at the Palais de Congres to exchange knowledge and ideas during educational seminars, workshops, networking sessions, and hands-on training.

Delegates attending the "PQLI – Global Realization and Implementation of the ICH Quality Vision" session had the opportunity to hear from senior regulators and industry leaders about latest developments in the implementation of ICH Q8, Q9, and Q10. See related article "PQLI Update from Strasbourg" by Dr. Kate McCormick.

Technology also played a pivotal role in the event. For the first time in Europe, select educational sessions were recorded – thus allowing the knowledge and experiences of the event to reach a wider audience – and are now available as downloadable webinars at www.ISPE.org/onlinelearning. Recorded sessions include Biological Products Manufacturing Challenges – Now and in the Future; Business Excellence Concepts, Process Development Improvements; Occupational Exposure Issues with Large and Small Molecules; and Risk-based Implementation of Single-use Systems. In addition, many of the seminars made use of voting technology to poll delegates, getting instant feedback on a number of questions posed by the audience.

In addition, it was the first time ISPE and INTERPHEX partnered to host a European vendor exhibition and a variety of networking receptions that allowed exhibit attendees to engage and network with fellow seminar delegates, vendors, and colleagues.

There was a unique opportunity to hear presentations by regulators from all three ICH regions and by industry leaders following the ICH meeting in Yokahama in June 2009.

Jean Louis Robert of Laboratoires National de Santé in Luxembourg and Chair of the Implementation Working Group, explained their role: to compile and publish Q&As; to organize training; and to develop case studies and joint publications.

There are three key topics. QbD is being led by the US FDA. Pharmaceutical Quality Systems (PQS) is being led from Europe. Knowledge Management (KM) is being led from Japan. In each case, a senior regulator presented the current situation.

Georges France of Wyeth Europa, UK and Bob Baum of Pfizer, USA gave the industry perspective. They reviewed benefits of the QbD approach, but emphasised the need for a change in culture across industry.

There were presentations on specific case studies currently being developed. Bruce Davis of Global Consulting, UK described an Illustrative Example (IE), which will demonstrate practical implementation of QbD in manufacturing and beyond. See related online exclusive article "Industry Meets Regulators for PQLI Update in Strasbourg" by Dr. Kate McCormick.

Graham Cook of Wyeth Pharmaceuticals, UK presented details of the Mock S2 project for drug substances. The purpose is to exemplify application of enhanced QbD concepts to the development and manufacture of both a traditional small molecule and a monoclonal antibody. Delegates received 'hot off the press' feedback from the latest training workshop organized by the EMEA PAT team, in conjunction with EFPIA.

Keith Pugh of MHRA, UK and chair of the PAT team described six real case studies presented during the workshop and highlighted a number of observations arising from the case studies.

Speaking on behalf of EFPIA, Georges France said there are challenges both for development/manufacturing and for assessors/inspectors.

Yukio Hiyama of the National Institute of Health Sciences, Japan presented recent changes to the pharmaceutical regulations and challenges presented by implementation of ICH Q8(R1), 9, and 10.

Emer Cooke, International Liaison Officer, EMEA described the significant role played internationally by EMEA and progress against the long-term vision of creating synergies through communication, collaboration, and cooperation to support a global approach to authorization and supervision of medicines.

Interactive workshops allowed comment on, and contribution to, current PQLI activities. Each workshop was lead by an industry representative and a regulator. Feedback from all workshops was presented in plenary session on the second afternoon.

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# Introducing the 2009-2010 Board of Directors

The following pharmaceutical industry professionals have been elected to positions on the 2009-2010 ISPE International Board of Directors:

***Chair:*** **Alan Mac Neice,** Ireland

***Vice Chairman:*** **Andre Walker,** Director, Manufacturing Engineering, BiogenIdec Manufacturing ApS, Denmark

***Treasurer:*** **Dr. Arthur (Randy) Perez,** Executive Expert, IT Quality Assurance, Novartis Pharmaceuticals Corp., USA

***Secretary:*** **Dr. Charlotte Enghave Fruergaard,** Senior Consultant, Finished Product Department, NNE Pharmaplan, Denmark

## New Directors

Each to serve the Society for a two-year term beginning 10 November 2009.

**Antonio Buendia,** Project Engineering Manager, Lilly SA, Spain
**Winnie Cappucci,** Quality and Compliance Computer Validation Specialist, Bayer Healthcare, USA
**Damian Greene,** Director/Team Leader, API Operations Team, Pfizer Global Manufacturing, USA
**Doyle R. Johnson,** Consultant, CDI Life Sciences, USA
**Morten Stenkilde,** Quality Director, Novo Nordisk A/S, China
**Andrzej Szarmanski,** Quality Director, Polpharma SA, Poland

## Directors in Place

The following Directors were elected in 2008 to serve a two-year term.

**Joan Gore,** Manager, Clinical Trial Packaging and Support Services, Eli Lilly and Co., USA
**Tomiyasu Hirachi,** Representative Director and President, EEM Japan Co., Ltd., Japan
**Stephen Tyler,** Director of Strategic Quality and Technical Operations, Abbott Laboratories, USA
**Dr. Guy Wingate,** Quality Director, GlaxoSmithKline, United Kingdom

## Past Chairman

The Past Chairman automatically serves one additional year on the Board.

**Charles P. Hoiberg,** Executive Director, Pfizer Inc., USA

# ISPE Announces Availability of A-Mab Case Study

ISPE has announced a major extension of its Product Quality Lifecycle Implementation® (PQLI®) initiative further into biotechnology. This development comes after the decision of the CMC-Biotech Working Group consortium to provide their A-Mab case study to ISPE. The public availability of the final version of this case study was announced during the PQLI session entitled, "Regional Regulatory Experiences Implementing the ICH Quality Vision" held on 10 November, during the Society's Annual Meeting in San Diego, California, USA.

"This marks a significant opportunity for PQLI," said ISPE President and CEO Robert P. Best. "We can now provide even greater support to the biotechnology community in the implementation of the advanced concepts of Quality by Design. We have plans to use it extensively around the world in discussions with industry and regulators throughout 2010 and beyond."

The CMC-BWG consortium comprises some 40 members from seven companies (Abbott, Amgen, Genentech, GlaxoSmithKline, Lilly, Medimmune, and Pfizer) and was established in 2008 to develop a case study illustrating how the principles of Quality by Design (QbD) can be applied to the development of biotechnology products, focusing on monoclonal antibodies. The A-Mab case study discusses the development of a monoclonal antibody and incorporates many advanced and aspirational QbD concepts.

"The CMC-BWG team has created an amazing and unique case study that is generating intense interest and excitement among the Industry and Regulatory Agencies around the world," said ISPE PQLI Project Manager, John Berridge, who served as one of the facilitators for A-Mab. "Many have questioned whether the principles of QbD are applicable to biotechnology. A-Mab answers that question with a resounding 'yes.' The mission was to describe a future state based on new ways of thinking and A-Mab definitely challenges the sometimes conservative ways industry does things today. We were constantly pushing the envelope to capture an aspirational QbD state showing enhanced product and process understanding. This is not a mock submission seeking regulatory approval. A-Mab provides many illustrative, sometimes controversial, examples of ways to implement QbD and will stimulate discussion about how the science supports these examples and how we can enhance future biotechnology product realization. This is an exciting 'next step' in the biotechnology work of PQLI."

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

# Latest Baseline® Guide Reviewed by the FDA Focuses on OSD Manufacturing Design and Construction


The newly released *Oral Solid Dosage Forms Baseline® Guide* addresses the latest interpretation of GMP requirements, as well as a risk-based approach to regulatory compliance relating to the design, construction, and validation of the OSD manufacturing facility.

This second edition is a revision of the original *Oral Solid Dosage Forms Baseline® Guide* published in February 1998. The revision includes an expanded product and processing chapter with detailed discussion of each critical unit operation and new technological trends, such as continuous processing and implementation of process analytical technology. The Guide provides a comprehensive view of best practices available in the pharmaceutical industry for oral solid dosage manufacturing facility design and construction. A lifecycle approach to project management is emphasized.

The following is the Table of Contents:

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- Electrical
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- Appendix 1 – Cost Factors in OSD Manufacturing
- Appendix 2 – Summary of Quality Risk Management Process
- Appendix 3 – Risk Management Tools
- Appendix 4 – HSE International Regulations and Standards Cross References
- Appendix 5 – References
- Appendix 6 – Glossary PE

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# Latest Baseline® Guide Reviewed by the FDA Focuses on OSD Manufacturing Design and Construction


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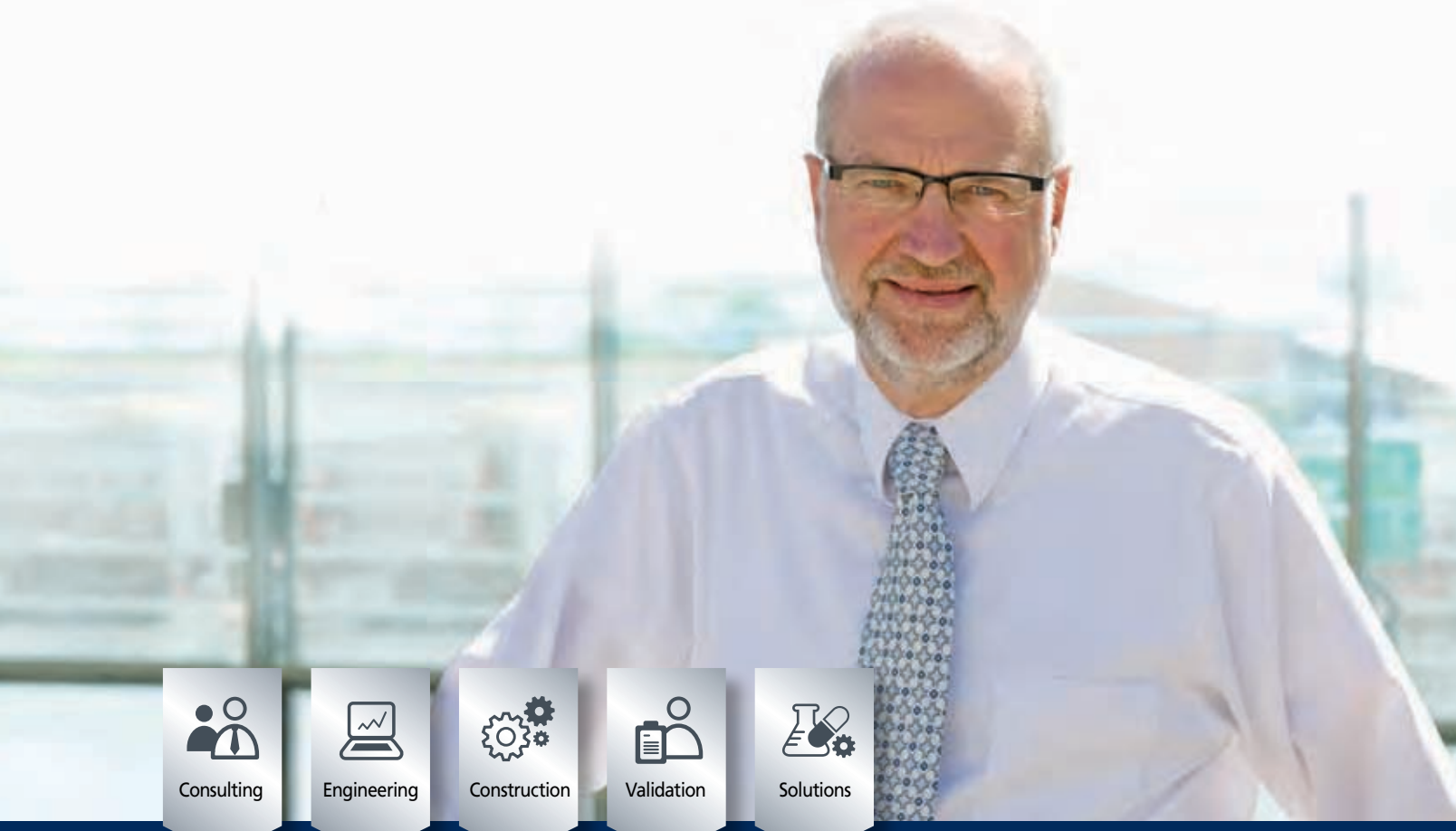

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# Industry Meets Regulators for PQLI Update in Strasbourg

by Dr. Kate McCormick

**This article presents the key messages from the presentations and conclusions from the PQLI workshops held in Strasbourg in September.**

ISPE held its European conference on "Managing Knowledge through Science and Risk Assessment" between 28 September and 1 October in Strasbourg. One of the seminars presented during the conference was PQLI® – Global Realization and Implementation of the ICH Quality Vision.

Over the course of two days, more than 60 industry representatives and senior regulators heard about the latest developments in ICH Guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Pharmaceutical Quality Systems). Additionally, a series of interactive workshops was used to gather views of delegates and move PQLI forward.

This article presents the key messages from the presentations and conclusions from the workshops.

## Influence of New Concept (QbD) on the European Pharmacopoeia (Ph. Eur.)

The seminar opened with a keynote address by Susanne Keitel of the European Directorate for the Quality of Medicines and Healthcare (EDQM) within the Council of Europe. She began with a short overview of the Council of Europe, which was founded in 1949 and has 47 member states, comprising more than 800 million people. She went on to reiterate that the role of a pharmacopoeia is to guarantee the quality of medicines by means of harmonized specifications, transparent monographs, and common reference standards.

Moving on to ICH Q8, Keitel sounded a note of caution. QbD is an optional approach, requiring high initial investment and uncertainty as to the returns expected. Therefore, even companies which adopt QbD may not wish to do so for all products in their portfolio. Therefore, there will be an ongoing need for a tiered system for both industry and regulators.

Keitel commented that flexibility is already written into the Ph. Eur. since it is not mandatory to carry out all monograph tests in order to release a batch. However, she emphasized that all batches must meet specification throughout their shelf-life.

She then went on to discuss Functional-Related Characteristics (FRCs) of excipients. Unlike the United States Pharmacopoeia (USP), which has put FRCs into a separate chapter, the Ph. Eur. deals with them in each monograph. There appears to be some concern within industry that regulators will take this as an indication that they are mandatory. However, Keitel stressed the non-mandatory section has been added to provide information that may be critical for functionality.

Keitel presented a round-up of the activities of the Ph. Eur. PAT Working Party, established at the request of the EMEA. Current activities include review and update of the general notices and general chapters and consideration of the relationship between sample size and acceptance criteria, taking into account the fact that PAT tools allow for much larger sample sizes.

In conclusion, Keitel stated that whatever system is chosen (QbD, design space, PAT, Real-Time Release (RTR), or a conventional approach to development and/or control strategy), safeguarding public health should be the first priority.

## ICH Implementation Working Group (IWG) Update

Delegates had a unique opportunity to hear presentations by regulators from all three ICH regions and by industry leaders on the current status of implementation of ICH Q8(R1), 9 and 10, following the ICH meeting in Yokahama in June 2009.

The session was opened by Jean Louis Robert

of Laboratoires National de Santé in Luxembourg who chairs the IWG. He explained that the role of the IWG is to compile and publish Q&As; to organize training; and to develop case studies and joint publications. To date, answers to 51 questions have been published and a further 11 are under discussion. Training, in the form of workshops to be delivered in all three regions during 2010, will take an integrated approach. There is an expectation that feedback from these workshops will form the basis of new Q&As. Case studies are being developed using material already in the public domain. However, additional topics are likely to be identified, which require collaboration between regulators and industry to produce position papers.

Following this introduction, three key topics were reviewed, each of which is being lead by a specific ICH region.

The presentation on QbD was given by Robert, on behalf of the US FDA. He reported that the new paradigm is clearly starting to be adopted. As of August 2009, there had been 34 applications to the FDA containing QbD elements (and the same trend is seen in Europe). It was acknowledged that these submissions included some challenging regulatory issues. Q&As have been developed to provide clarification on the topics of design space, real-time release testing, and control strategy. Additional questions also can be submitted via the ICH Web site.

It was reiterated that the regulators are completely dedicated to the new approach. However, as a word of caution, it was emphasized that the patient should not be ignored for the sake of technical innovation; for example, the dosage form should be user friendly. Also, industry was urged to remember that QbD is not a slogan and that companies need to explain the rationale behind their submissions.

The topic of Pharmaceutical Quality Systems (PQS) is being led from Europe and this part of the presentation was given by Jacques Morénas of AFSSAPS. He started by pointing out that while PQS may be a new concept for development, it is well-established within manufacturing and will be covered as part of GMP compliance inspections. It also will be inspected at the request of assessors as part of the marketing authorization evaluation, but the PQS should not form part of the submission dossier. The presentation concluded with emphasis on three elements which should not be underestimated: the need to use ISO terminology to facilitate understanding between all stakeholders; the involvement of senior management; and the management of outsourcing activities.

The topic of Knowledge Management (KM) is being led from Japan and this part of the presentation was given by Yukio Hiyama of the National Institute of Health Sciences in Japan. He pointed out that KM is not new and is important whatever the approach taken to development. However, the more complex information generated by the new approaches will need to be captured, managed, and shared during the product life-cycle. He gave some interesting observations of poor KM, as seen during inspections and commented on the excessive time taken by some companies to respond to CMC questions.

Speaking on behalf of industry, Georges France of Wyeth Europa, UK returned to the questions raised earlier by Susanne Keitel. He reviewed the benefits to industry of adopting the new approach. While it is true that it requires investment, benefits can be obtained from the beginning and will be ongoing. While the principles of both approaches are the same, the sophistication of the new approach allows deeper investigation and hence a better understanding of the manufacturing process.

Closing the session, Bob Baum of Pfizer, USA posed the question: why are we going through this process; why is implementation taking so long? It's not because the authors didn't know what they were doing. It's more a case of needing to assure global consistency. While early ICH guidelines were based on knowledge and experience, recent ones deal with approaches which are new to pharmaceuticals, even if well-established in other industries. In his view, while ICH Q8, Q9, and Q10 are optional, there will be a time when the traditional approach will be the optional exception, rather than the norm for most companies.

Baum concluded by stating that 'culture will eat strategy for lunch.' It took Juran and Deming more than 20 years to establish a culture of quality within Japan. In order to establish the new paradigm as the established paradigm, it is necessary to change the culture within the pharmaceutical industry.

## Examples and Case Studies

There were two interesting presentations on specific case studies being worked on by industry sub-groups. Bruce Davis of Global Consulting, UK gave details of the Illustrative Example (IE), which is currently under development. He emphasized the work was only at a draft stage and not ready yet for publication.

The team is using the European Federation of Pharmaceutical Industries and Associations (EFPIA) model, which is a good summary of QbD, and looking at practical implementation in manufacturing and beyond. However, it must be stressed that this will be an example only; not a definitive methodology. The IE will describe the development and manufacture of a product (both substance and finished dosage form) based on a new small molecule. Delegates were shown drafts of a detailed case study, including manufacturing flow diagrams, product profiles, and risk assessments. One objective is to demonstrate how products developed using QbD can be implemented within manufacturing and the implications for the existing PQS. Davis concluded by saying this was a tremendously complex project which had generated much discussion, but also much excitement about the globalization of PQLI.

During the Q&A session following this presentation, John Berridge, ISPE Regulatory Advisor announced that ISPE will be participating in an exciting new project to develop a biotech case study as well.

Graham Cook of Wyeth Pharmaceuticals, UK then presented details of the Mock S2 project for drug substances, sponsored by EFPIA. This project arose out of the EFPIA Mock P2 document published in January 2006, which illustrated how QbD could be applied to an oral tablet. The new

project is to develop similar discussion documents for the application of enhanced QbD concepts to the development and manufacture of both a traditional small molecule and a monoclonal antibody (large molecule).

The large molecule document is at the editing stage. Feedback is being sought from stakeholders, including regulators, EFPIA member countries, and other industry organizations. Publication is expected late 2009 or early 2010. The small molecule document is more advanced and publication is expected late 2009. Again, it was emphasized that these were illustrations, not definitive solutions. Cook reminded industry that assessors are key customers and companies should identify what they need to see and in what way they need to see it. In particular, an initial summary will help before going into the detail of the submission.

## EFPIA and PAT Team – Training Initiative Based on Real QbD Examples

The second day of the seminar began with 'hot off the press' feedback on the training workshop held over the previous two days in London by the European Medicines Agency (EMEA) PAT team, in conjunction with EFPIA. The PAT was established five years ago in response to ICH.

Keith Pugh of MHRA, UK and Chair of the PAT team, described the training workshop, the latest in a series run since 2007. Day 1 involved more than 100 people, as six companies (out of a much larger number that applied to take part) presented real examples of their QbD projects to inspectors and assessors in closed sessions. On Day 2, an open session providing feedback from Day 1 was attended by 250 people.

Pugh then went on to provide an overview of the six case studies: Integrated Application of a QbD Development Approach Across Chemical and Formulation Manufacturing Process (Merck Sharp and Dohme); Continuous Quality Verification, an Approach to Process Validation (Pfizer); Use of In-line NIR Spectroscopy to Monitor Segregation of a Pharmaceutical Powder Blend in a Tablet Press (Lilly); the Use of In-vitro and In-vivo Data to Define both Design Space and Control Strategy (Astra-Zeneca); QbD Development of a Novel Therapeutic Protein (Wyeth); and Utilization of QbD Principles for the Management of Post Approval Changes for a Novel Recombinant Monoclonal Antibody (Amgen). Summary slides for the whole of Day 2 are available on the EFPIA Web site (http://www.efpia.org/content/Default.asp?PageID=704).

Pugh made a number of observations based on these case studies: growing use of models and trending; the large amount of data generated by NIR which needs to be summarized; the importance of defining design space appropriately; and the fact that risk ranking is more prominent in discussions on large molecules than small ones. QbD can be described, if not as a revolution, at least as a serious evolution.

Speaking on behalf of EFPIA, Georges France said there are challenges both for development/manufacturing and for assessors/inspectors. The quality of science comes up in all discussions. He went on to emphasize three key points made already by previous speakers: the importance of a summary at the start of a submission; the need in Europe for the PQS to provide support for the Qualified Person (QP); and the fact that QbD also is valid for biopharmaceutical products.

The outcome of the training workshop will be shared with the ICH IWG at an appropriate point in order to move toward international agreement on the issues raised.

## Global Challenges – Japan and Beyond

Yukio Hiyama gave an interesting presentation on recent changes to the pharmaceutical regulations and challenges presented by implementation of ICH Q8(R1), Q9, and Q10. The 2002 revision of the Pharmaceutical Affairs Law is currently being implemented and will be completed in 2010. Changes to the law include: revision of the licensing system from manufacturing and importation approval to marketing approval; the introduction of Good Quality Practice (GQP); introduction of control of materials into the approval process; and GMP as a prerequisite for product approval. Hiyama pointed out that English translations of the Good Quality Practice (GQP) and GMP ordinances are now available on the internet (http://www.pmda.go.jp/english/services/reviews/ordinance.html)

Issues relating to ICH Q8(R1), Q9, and Q10 implementation include: the legal changes are taking Japan toward Q10 requirements; the focus for GMP inspectors is moving from EU/USA to Asia, specifically APIs for generics; discussions are in progress on module 2 of the CTD and a mock P2 (Sakura Tablet) has been published. Particular difficulties have been found in communication between Marketing Authorization Holders (MAH) and contract manufacturers due to inadequate contracts. It has been observed that there is insufficient concern by Japanese MAHs in control of manufacturing in foreign sites.

## Global Challenges for EMEA Liaison in the International Regulatory Context

The last speaker of the seminar was Emer Cooke, who has recently taken on the role of International Liaison Officer within EMEA. She described the significant role played internationally by EMEA, the 11 key objectives published by the European Commission (EC) in December 2008 and progress to date. The long term vision is: creating synergies through communication, collaboration, and cooperation to support a global approach to authorization and supervision of medicines.

Cooke went on to discuss the program of activities underway between EMEA and FDA. Achievements to date include: agreement on principles for joint genomic data submission and interaction on pediatric therapeutics and a GCP pilot initiative. The Transatlantic Administrative Simplification (TAS) initiative has lead to commencement of joint inspections in respective territories. While these still lead to individual reports being issued, these reports will have common findings, conclusion, and follow-up. EMEA and FDA also are collaborating in plans for third-country inspections.

Other international activities include: support to the EC in working with third countries, such as India and China; negotiation and implementation of Mutual Recognition Agreements (MRAs); participation in international forums such as ICH; and cooperation with WHO.

## Interactive Workshops

Throughout the two-day seminar, a series of interactive workshops were held, to allow delegates to comment on and contribute to, current PQLI sub-group activities. In each case, the workshop was lead by an industry representative and a regulator. Feedback from all workshops was presented in plenary session on the second afternoon.

Workshop A, the pharmaceutical supply chain, was lead by Janeen Skutnik of Pfizer, USA and Yukio Hiyama. While raising the question of whether there is over-reaction to recent incidents, it was concluded there is justification for incorporating some elements of supply chain into the IWG Q&As and the PQLI Roadmap. The concept of geopolitical scanning also was introduced as a potential tool for information-sharing.

Workshop B, QbD in the manufacturing environment: control strategy from development to manufacturing to enable batch release, was lead by Line Lundsberg of NNE Pharmaplan, UK and Jacques Morénas. It was concluded that control strategy is not new and is required for both conventional and QbD approaches; also that control strategy and batch release are not the same. Important elements include training and cultural change. Everyone, including the operators, need to understand which aspects of the manufacturing process are critical.

Workshop C, RTR Testing: What is Needed for Quality Control?, was lead by Graham Cook and Susanne Keitel. It was concluded that RTR does not imply the elimination of end-product testing; nor should there be two different specifications. Rather, it is an alternative methodology to demonstrate compliance with the required specification. The role of the QP will be essentially unchanged although there may be some new considerations. The presentation of the control strategy in the dossier will be an important factor.

Workshop D, Biotech topics including CQA/CPP, was lead by Ranjit Deshmukh of Wyeth, USA and Keith Pugh. It was concluded that the decision-trees are relevant for large molecules as well as small ones. In terms of process qualification, some measure of process robustness evaluation is necessary; data from small scale and large scale batches can be mixed; and qualification does not need to be performed at the center point, provided parameters are within the qualified design space.

Workshop E, Knowledge Management Across the Life Cycle, was lead by Mike James of GSK, UK and Jean Louis Robert. It was concluded that there are challenges due to increasing complexity and the ability to recognize and retrieve critical data. Knowledge transfer is traditionally from development to manufacturing only, but feedback loops must be established. Issues are associated with submission of data and assessors need to be told from where knowledge has been derived. Inspections will not be used to evaluate data. Finally, it was emphasized that information sharing also must be a two-way process between industry and regulators.

Workshop F, Pharmaceutical Quality System from Development to Manufacturing Supporting an 'Enhanced' Submission, was lead by Nigel Hamilton of Sanofi Aventis, UK and Jacques Morénas. It was concluded that a well-designed and operated company PQS should be capable of supporting both minimal and enhanced submissions throughout the product lifecycle. The proof of this will always be determined at site/local level.

## About the Author

**Dr. Kate McCormick** of Heathside Information Services Ltd, United Kingdom, is a manufacturing consultant with extensive strategic and operational management experience in the pharmaceutical industry, both in the UK and internationally. She has 10 years of line management and 20 years of internal and external consulting experience. She has worked with multinationals, SMEs, non-governmental organizations, and national regulatory authorities in more than 50 countries. She is the author of Quality (a textbook within the Butterworth Heinneman pharmaceutical engineering series) and Manufacturing in the Global Pharmaceuticals Industry, the editor of gmp Review and a regular speaker at international conferences. McCormick gained a degree in biochemistry and a doctorate in microbiology, both at London University. She also has a Masters in Business Administration. She is registered as a senior GMP expert within the EU and is eligible as a QP under the terms of the EU directive. She is currently European Education Advisor for ISPE. She can be contacted by telephone: 44-1626-854611 or by email: kate@heathside.com.

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