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JANUARY/FEBRUARY 2012 VOLUME 32, NUMBER 1

In this issue, feature articles on

## Trends in Quality and Compliance

including

**Alternative Software Development**
**Quality Risk Management**
**Gravimetric Sample Preparation**
**Risk-Based Approach to Cleaning Procedures**

plus

**MedImmune's Winning Facility of the Year Project**

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# Table of Contents



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PHARMACEUTICAL ENGINEERING®

THE OFFICIAL MAGAZINE OF ISPE

JANUARY/FEBRUARY 2012 VOLUME 32, NUMBER 1


## Cover Photo

Photo courtesy of MedImmune.

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## Departments



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**This article presents the story of how MedImmune used ordinary tools in extraordinary ways to build the MedImmune Frederick Manufacturing Center Expansion, Overall Winner of the 2011 Facility of the Year Awards.**

# Case Study: MedImmune's Frederick Manufacturing Center (FMC) Expansion, Overall Winner, 2011 Facility of the Year Awards

## *Precision Planning for Innovation*

by Rochelle Runas, ISPE Technical Writer

### Introduction

Before announcing the Overall Winner of the 2011 Facility of the Year Awards (FOYA) to hundreds gathered at the ISPE 2011 Annual Meeting in Texas, USA, Chaz Calitri, Chairperson of the FOYA Judging Panel, quoted the late Steve Jobs:

> *"Creativity is just connecting things. When you ask creative people how they did something, they feel a little guilty because they didn't really do it, they just saw something. It seemed obvious to them after awhile. That's because they were able to connect experiences they've just had and synthesize new things."*

It's fair to say that those who worked on the Overall Winning project knew exactly what Jobs was talking about, and then took that concept a step further. This article presents the story of how MedImmune used ordinary tools in extraordinary ways to build the MedImmune Frederick Manufacturing Center Expansion, Overall Winner of the 2011 Facility of the Year Awards.

### Project Overview

MedImmune, the global biologics arm for AstraZeneca PLC, currently has more than100 products in its research and development portfolio. To enable the future production of products from this robust pipeline, MedImmune chose to expand its Frederick Manufacturing Center (FMC) in Frederick, Maryland, USA. The new facility houses 337,000 square feet of administrative, production, warehouse, laboratory, and utility space. To accommodate future growth, MedImmune designed internal expansion capabilities of an additional 100,000 square feet of production space, creating a flexible, large-scale mammalian cell culture-based production facility.

The facility received licensure in June from the US FDA for the manufacture of Synagis® (palivizumab), a drug to help protect high-risk premature infants from severe Respiratory Syncytial Virus (RSV) disease.

"The licensure of Building 633 represents a prime example of collaboration and flawless execution across a large enterprise. As I look back, there is no single function at MedImmune that I can said did not play an integral role in contributing to the ultimate success of this project," said Greg Liposky, Vice President and General Manager of Operations at FMC.

While there are a number of large-scale mammalian cell culture bulk production facilities in the industry, the ability to accommodate products with a broad titre range and the flexibility built into expansion makes the MedImmune Frederick facility one of the largest single bulk bio production assets in the industry.

The facility and project is notable in several ways:

*Continued on page 10.*

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- They chose to design what MedImmune believes is the first large-scale facility in the industry able to produce a broad base of products with titres ranging up to 7.0 grams per liter.

- They implemented a best-in-class Process Control System (PCS).

- In a short period of time, they transitioned manufacturing operators from a small scale, single product, semi-automated facility to a large scale, multi-product, highly automated facility.

- They provided operators a significant amount of on-the-job training before the start of Process Validation (PV) runs to ensure the validation program was successful.

- Flawless execution of the shakedown and process validation runs resulting in (16) 15K bioreactor batches without a single contamination.

## Implementing a Best-in-Class Process Control System (PCS)

The sheer magnitude of the facility dictated the high complexity of the PCS. The team decided that the PCS platform would be based on the Rockwell family of hardware and software. The PCS is a fully integrated, custom installation, designed as a GAMP 5 – Category 4 system. The design of the PCS encompasses the following capabilities:

- Control, monitoring, alarming, and data collection of:
  - 44 production skids
  - all process piping and transfer panels, and holding tanks
  - clean-in-place equipment
  - steam-in-place equipment
  - critical utilities

- Integrated communications with the building management system

- Design to allow:
  - future expansion to implement a second full manufacturing module
  - for ease of transfer to Electronic Batch Record (EBR) methodology
  - for plug and play integration with Manufacturing Execution Systems (MES)

- Use of a common Human-Machine Interface (HMI)

MedImmune faced several typical challenges implementing a system of this type and magnitude, but met them with unique solutions:

### *Challenge: Plan a solid system integration of all skids from a multitude of vendors.*

To integrate 44 skids from more than 12 countries, the team operated under *"a common control system for all"* mission statement. They planned for a modular approach to integration and engaged all equipment skid manufacturers early in the PCS development process. Although they used the S88 model, which is nothing new in itself, the team realized that each vendor played a part in the overall solution. The skidded systems were organized by criticality to the process:

- **Type 1: Process Manufacturing Systems** were the most critical, requiring that these system controllers be programmed using common modules. In keeping with the S88 standard, this approach started with the lowest level of the S88 equipment model – the Program Logic Control (PLC) modules. These modules control, monitor, and alarm devices such as valves, motors, PID loops, and analog alarms.

  The system integrator developed and tested the modules using its pre-existing code library, with specific modifications as required for the project. The PLC modules were then turned over to each critical equipment or skid vendor, and training was provided on how to leverage the modules into the overall application logic for that skid. The Factory Acceptance Test (FAT) for each skid verified the use of the control modules, as well as the integration of the PLC application with the overall PCS HMI/SCADA system, developed for the entire PCS by the system integrator.

- **Type 2: Manufacturing Process Support Systems** were deemed less critical. These equipment vendors were directed to leverage their standard application logic and did not incorporate the project-standard control modules. However, these equipment systems were incorporated into the PCS by utilizing the overall PCS as their HMI/SCADA

| Type 1 System | Qty | Type 2 System | Qty | Type 3 System | Qty |
|---|---|---|---|---|---|
| Bioreactors | 10 | Parts Washers | 4 | Gray Water System | 1 |
| Chromatography | 2 | Autoclaves | 3 | Carbon Absorption System | 1 |
| UF/DF | 1 | | | Pure Steam Generators | 2 |
| CIP | 6 | | | Instrument Air Dryer | 1 |
| Centrifuge | 2 | | | WFI Generation Stills | 2 |
| Viral Filtration | 4 | | | Multi Media Filter Skid | 1 |

Skidded systems organized by criticality to the process.

*Continued on page 12.*

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system. This approach allows operators to use one HMI to operate, control, and monitor all systems, drastically reducing the time needed for operators to understand and operate systems.

- **Type 3:** These systems were the least critical equipment systems. These system controls were not incorporated into the PCS; however, the skid vendors were required to "tag" all data and alarm points within their controllers to allow centralized monitoring of all systems. Each vendor provided their standard application logic as well as their standard local Operator Interface Terminal (OIT). This allowed the PCS to capture alarms and data and display the alarms on one common platform.

### *Challenge: Support simultaneous start-up and debugging of the PCS.*

A common issue in automation projects, especially of this size, is interfacing skidded systems with the PCS and with each other. "Traditionally, nothing talks and nothing works and you can spend months upon months trying to solve intersystem communications issues," said Brent Hill, Director of Automation, Global Engineering, MedImmune.

Using a proactive approach to solve this potential issue, the team developed a Factory Acceptance Test Process Automation Core (FATPAC), a portable interface package to support FAT. This package of servers replicated MedImmune's high-level process network and allowed MedImmune to test the equipment in their own environment, at each vendor site.

### The FOYA Factor

***"This project was a tremendous success and is reflective of the ingenuity, creativity, and commitment shown by the entire project team. They did a masterful job in delivering this challenging and complex project."***

– Doug Scott, Vice President, Global Engineering & Facilities, MedImmune

***"I can't think of a better way to congratulate all the team members. We worked hard and this is validation for everyone."***

– Brent Hill, Director of Automation, Global Engineering, MedImmune

***"As an engineer, it's like winning the Oscar, or the closest thing to it. The greatest joy I have is to build a facility and see products go to market that help patients."***

– Aaron Vernon, Associate Director of Cost & Schedule Engineering, Global Engineering, MedImmune

The FATPAC included a domain controller used to preset user access, a PLC, and an HMI client from the PCS system. Communications were set up with the PCS PLC/HMI and used in the FAT for each of the skids. Any problems were identified during FAT, resolved, and retested prior to shipment. "When the skids arrived on site, there was minimal setup required to integrate them into the PCS system," said Hill. "We shaved a good six to seven months of typical delays in start-up, such as commissioning and validation groups waiting on interface issues."

### *Challenge: Maintain change control over the integrated PCS code during simultaneous start-up of multiple systems.*

During automation system start-up in a cGMP environment, it is typical practice to leverage work completed in FATs, installation, and commissioning. More often than not, these activities are limited to hardware IQ checks. Functional OQ test validity is always in question due to lack of code control. Installation and testing of a system this size, with 7,000,000 lines of automation software code and 44 different skids, is a daunting task to manage. In addition, the leveraging strategy dictated by MedImmune added a complexity to start-up activities, which posed a major challenge to the team: how to track, maintain, and control PCS code revisions while simultaneously performing leveraged start-up activities.

To proactively address this problem, the automation group used an off-the-shelf Rockwell configuration management application to manage coding. The tool, which has automatic revision control, requires programmers to "check out" code from a repository. This allows an auditor to go back to any point in time and see what changes were made to code throughout the development and testing process.

"While the tool itself is not unique, we did turn it on relatively early and utilized it right after FATs," said Aaron Vernon, Associate Director of Cost & Schedule Engineering, Global Engineering, MedImmune. The team created a Configuration Management Plan at the onset of planning. This document set the process for managing all application files with the key aspect of the plan being the configuration management tool.

The use of an automated configuration management tool quickly proved valuable during commissioning and start-up, because many changes were identified and implemented during this phase. For example, 15 control engineers were accommodating various change requests to the PCS code.

The process continued through validation with a parallel test system configured as a mirror image of the production system that was being validated. Following validation of each skid or process area, the associated code was versioned again and an automatic schedule for upload and compare was established.

This schedule provided for automatic comparison of the actual code running in the production system to the locked, effective, master version. Any differences between the two

Part of the dedicated training lab.

versions initiated an automatic log and email notice to key team members, said Vernon.

In addition to control of PCS code, this automated configuration management system has been used to control batch file configuration management.

### *Challenge: Create and deploy operator training to a wide audience with varied levels of experience with automation controls.*

MedImmune needed to transition manufacturing operators accustomed to a small-scale, single product, semi-automated facility to a large-scale, multi-product, and highly automated facility. This had to be completed in a short period of time without risking equipment damage to any critical process and support systems or risking loss of product materials due to incorrect use of the PCS.

The solution: a four-tiered, blended learning approach commonly used in the military, but rarely implemented in the biopharmaceutical industry. This approach was developed as a collaborative effort between a number of site and corporate functions, and included:

- **Concept Training** – concept training consisted of interactive Computer Based Training (CBT), which allowed employees to gain a general understanding of how the facility and the process control system would operate. The CBTs, developed according to successful adult learning theories, clearly state the training objectives, and then lead the student from overview and concept understanding to higher-level knowledge of the PCS. The CBTs included detailed checks for understanding after completion of each module. Also included were Printable Quick Reference Guides to be used as job aids while using the PCS HMI. These guides included information on the PCS structure, User Access Rights, a summary of alarm conditions, locations of PCS stations throughout the building, and definitions of terms.

- **Review of Operational SOPs** – this component involved the requirement of students to review the SOPs as preparation prior to attending hands-on training.

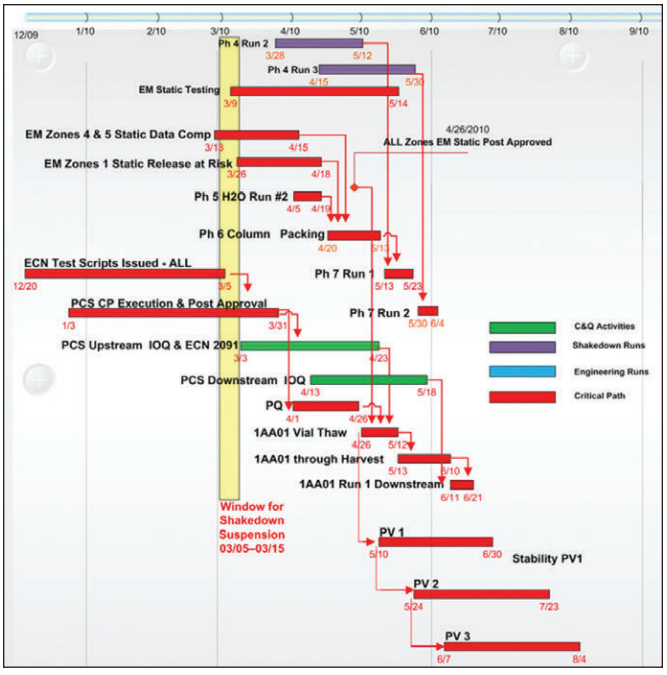
- **Hands-On, Instructor-Led Training** – a dedicated training lab was built by creating a pared-down version of the PCS. The lab included a subset of the process control functionality found on the manufacturing floor. The lab allowed operators to train on a "live" system that looked, felt, and behaved like the real PCS. A series of instructor-led sessions which mirrored actual production scenarios were also were created. These sessions allowed operators to use the PCS HMIs to perform tasks, such as media preparation, transfer operations, and cell culture, harvest, and purification operations.

- **On the Job Training with a PCS Simulator** – the project team understood that proficiency on the live system would require additional practice using the PCS. To minimize knowledge loss between operator training and live PCS usage, the project team developed a PCS Simulator for all operators who had completed the instructor-led training in ICQ activities. Use of this simulator helped ensure proper use of equipment through the PCS.

"This robust training developed to assure initial validation run success continues to provide value to the organization. It has become the foundation of our current training program at the site," said Liposky.

## The Art of Start-Up: Progressive Shakedown and Process Validation Methodology

The start-up, process shakedown, and process validation schedule was optimized to meet the schedule requirements of the project. More importantly, they utilized an approach to get exposure to the systems as soon as possible for experience




Integrated shakedown methodology.

*Concludes on page 14.*

## Facility of the Year Awards

Sponsored by ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine, the Facility of the Year Awards (FOYA) program recognizes state-of-the-art pharmaceutical manufacturing projects that utilize new and innovative technologies to enhance the delivery of a quality project, as well as reduce the cost of producing high-quality medicines. Now in its eighth year, the awards program effectively spotlights the accomplishments, shared commitment, and dedication of individuals in companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of patients.

More information on the Facility of the Year Awards program can be found at www.FacilityoftheYear.org.

• • •

### *2011 Facility of the Year*

**MedImmune's Frederick Manufacturing Center (FMC) Expansion**, category winner for *Project Execution*, was selected as the Overall Winner of the 2011 Facility of the Year Awards among five other Category Winners in 2011. A sixth facility was selected to receive an Honorable Mention. The winning companies and respective award categories are:

- **Merck & Co., Inc.**, winner of the Facility of the Year Award for *Facility Integration* for its Global Clinical Supplies Manufacturing, Packaging and Warehouse expansion project in Summit, New Jersey, USA
- **Novartis Vaccines and Diagnostics GmbH**, winner of the Facility of the Year Award for *Equipment Innovation* for its "MARS Project" (Marburg Site) facility in Marburg, Germany
- **Pfizer Health AB**, winner of the Facility of the Year Award for *Operational Excellence* for its Project Pegasus – Bio 7 Manufacturing facility in Strängnäs, Sweden
- **Pfizer Manufacturing Deutschland GmbH**, winner of the Facility of the Year Award for *Sustainability* for its SPRING and E-MAP (Strategic Plant Restructuring and Energy Master Plan) project in Freiburg, Germany
- **Shire HGT**, Facility of the Year Award *Honorable Mention* for its Project Atlas, Building 400 facility in Lexington, Massachusetts, USA

and knowledge. To meet this challenge, the team planned for successive shakedown runs several years in advance.

Each successive shakedown run phase utilized more equipment than the previous phase and started concurrently with ICQ activities. The shakedown phases separated unit operations to allow for complications, problem-resolution, and gain experience particular to each unit operation.

The approach also maximized operator on the job training, said Vernon. "The shakedowns were as much training for our people as it was testing of equipment."

The project team successfully completed 13 shakedown runs and three PV runs without a single contamination or lost batch. More impressive is that for every batch, MedImmune met all product and process metrics. From the first batch in the production bioreactors, viable cell density, cell growth, and product titer closely matched the average results for more than 200 batches run prior at MedImmune and 20 batches at a contract manufacturing organization.

## Offline Integrated Commissioning and Qualification (ICQ)

As shakedown activities took precedence in the schedule, it was necessary for the project team to perform activities related to the commissioning and qualification of the PCS in parallel, without interrupting shakedown runs. Under the strain of limited time on equipment as a result of competing project phases (start-up and debugging of applications, train production operators, and running test batches), the project team developed a separate PCS simulator (in addition to the PCS simulator used for operator training) that allowed them to commission and qualify major aspects of the PCS without having to perform the work on the plant floor. This system, which simulates every Programmable Logic Controller (PLC) in the facility, provided a safe, equivalent environment to perform testing. Today, this simulator is used for qualification and tech transfers, says Hill.

## Stellar Safety Record

The project was completed with a safety record of more than 2.3 million man-hours without a lost time incident. "For a complex project of this size and scope, the 2.3 million hours without a lost time incident is an impressive achievement. Worker safety was the highest priority for us, and required extensive collaboration, from the project leadership to the construction workers," said Doug Scott, MedImmune's Vice President of Global Engineering.

## Conclusion: Focus on the Front-End

The FOYA Judging Panel was impressed by MedImmune's solid planning, risk management, and creative problem resolution, earning MedImmune earlier in the competition the Category Award for Project Execution. These characteristics of robust project management fueled MedImmune's fast-paced, but efficient execution of implementing its innovative start-up and operator training and unique process for offline validation.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**This article presents methods used for the development of all types of software, from infrastructure software to bespoke applications.**

# Alternative Software Development Models and Methods in GxP Environments

by the Members of the ISPE GAMP D-A-C-H SIG ASDMM

The GAMP® Guide's[1] definition of the system lifecycle establishes good practice for computerized systems in regulated industries from the perspective of the regulated company. It also describes good supplier practices and typical documentation practices. The unique quality requirements in the healthcare and life science industries demand a transparent, systematic, verifiable, and documented life cycle. For this reason, the GAMP 5 Guide illustrates computerized system projects following a generalized specification and verification model, based on a V diagram, where each stage (e.g., specification, configuration and/or coding, and verification) is supported by appropriate documentation with a clear correlation between the specification and verification stages.

In the past 10 to 15 years, software suppliers have introduced new software development tools and project management methodologies in order to increase the amount of iteration and interactivity in the development process. As a result, the healthcare and life science industries are being confronted with these new methods. With the publication of the GAMP 5 Guide in 2008, use of these new models and methods is explicitly mentioned:

*"The approach described in this document is designed to be compatible with a wide range of other models, methods, and schemes, including: Software development methods, such as Rapid Application Development (RAD), Agile, Rational Unified Process* (RUP), or Extreme Programming (XP)."*

The GAMP D-A-CH (Germany, Austria, and Switzerland) Special Interest Group "Alternative Software Development Models and Methods" (ASDMM) convened to describe how these new tools and methods could be used in the development of validated computer systems.

The methods discussed in this document can be used for the development of all types of software, from infrastructure software to bespoke applications. Further, the healthcare and life science industries will be confronted with these methods when conducting audits of commercial software vendors, who may use these methods in developing software products.

From many incremental and iterative software development and project management methodologies in use today, the following were selected for closer evaluation as they are in widespread use and as such, there was first-hand knowledge and experience available in the working group. This list represents some of the most commonly used methodologies – it is by no means comprehensive or exhaustive. The following methods were evaluated:

- Scrum
- Extreme Programming (XP)
- Iterative Conference Room Pilot (CRP) (also commonly referred to as rapid prototyping)
- Model Driven Architecture (MDA)

The authors' goal was to determine if these methods can satisfy the regulatory requirements for software development and if so, provide guidance to software producers and users on how the alternative development methods can be used to develop software intended for use in regulated environments. The focus of this evaluation was to determine what documentation is produced as an inherent part of the selected methodology and to analyze the gap compared with typical

documentation as described in GAMP 5.

This is not a detailed study or comparison of the specific methods; however, to learn more about each of these methods, please consult the referenced materials listed in the bibliography at the end of this article.

## Comparison with Typical GAMP 5 Documentation

In order to find out if the selected methodologies are suitable to support the development of software for use in the health care or life sciences industries, the documents specified or created by each methodology will be compared to the typical development documents as described in GAMP 5.The GAMP 5 documents are mapped into five generic categories - *Table A*.

With the mapping of the methodology-intrinsic documents into these generic categories, it will be possible to evaluate the usability of each methodology in GxP regulated environments.

| Document Category | Individual Documents in GAMP 5 |
|---|---|
| Requirements | User Requirements Specification (URS)<br>Functional Specification (FS) |
| Design | Design Specification (DS)<br>Module Design Specification |
| Implementation | Code Review |
| Design Verification | Unit/Module-Tests, Integration Tests,<br>Functional Tests |
| Requirements Verification | Requirements Tests |

Table A. Document categories in the evaluation.

## The Methods in Detail

### *Scrum*

#### *Introduction*

Hirotaka Takeuchi and Ikujiro Nonaka originally proposed scrum as a product development methodology in a *Harvard Business Review* article "The New Product Development Game."[2] The Scrum software development methodology was first described in the book "Wicked Problems, Righteous Solutions: A Catalog of Modern Engineering Paradigms."[3]

#### *Description of the Methodology*

The Scrum methodology is designed as follows - *Figure 1*.

- The common goal (sprint goal) is defined by the product owner (who has budget responsibility).
- The functionality of the product (product backlog) is defined by the Product Owner.
- The effort to develop each function is estimated by the team (self-organized).
- The selection of individual product backlogs for the next development cycle (sprint backlog) is defined by the team.

*Continued on page 18.*

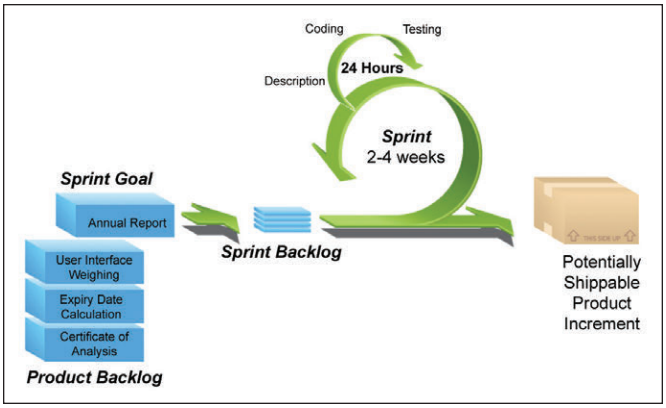


Figure 1. Sprint process.

- Execution of the sprint backlog by the team with a daily review of the work progress and any necessary adjustments.
- Review of the sprint backlog together with the product owner (frequency determined by the contents of the sprint).

### *Applicability in GxP Environments*

Documentation

The following documents are maintained in a scrum project:

- The product backlog is initially defined by the product owner and lists the required functions of the product. The product backlog need not be completely defined at the beginning of the process, as it can be updated at any time. At the beginning of each sprint (development cycle), the priorities of the product backlog are reviewed and adjusted as necessary.
- The sprint backlog lists those functions, which have been selected for the next development cycle (sprint).
- The Burndown Chart illustrates the amount of work remaining in a sprint.
- The Impediments List documents all barriers, which impeded progress during the development.

The following describes the use of scrum in GxP relevant environments:

- **Positioning of Scrum in the Software Life Cycle (SLC)**
  Scrum is not a classic software development methodology, as it does not specify any coding standards or methods, nor does it provide templates for project documentation. Scrum describes the roles and responsibilities for the development and sets a framework for the management of the requirements and project life cycle.

- **Use of the Deliverables of the Scrum-Methodology in the SLC**
  The product backlog (function list) can be considered as an equivalent to the user requirements specification. In this sense, the sprint backlog is a selection for the next sprint period, but also can contain additional descriptions that can be considered as the base for the functional specification and will be on a monthly basis.

| No. | GAMP 5 Development Document | Document Name or Activity | Comment |
|---|---|---|---|
| 1. | Requirements | Product Backlog | Represents the User Requirements Specification, which is constantly being revised. The Product Backlog should be structured as described in GAMP 5, Chapter D1. |
| | | Sprint Backlog | A selection and refinement of the Product Backlog that represents additionally the Functional Specification. The Sprint Backlog should be structured as described in GAMP 5, Chapter D2. |
| 2. | Design | --- | --- |
| 3. | Implementation | --- | --- |
| 4. | Design Verification | --- | --- |
| 5. | Requirements Verification | Review by the Product Owner | The 4-hour Review meeting is held at the end of each Sprint (monthly). |

Table B. Comparison scrum – typical documentation.

When scrum is combined with the contents, which the GAMP Guide recommends for the user requirements specification and functional specification, scrum can offer a significant quality benefit over sequential methods (how the V model is often used in practice) – the requirements are reviewed and appended periodically throughout the development lifecycle - *Table B*. This implies that there must be a high level of trust between the customer and the software developer; however, without detailed requirements at the outset of the project, it is impossible to estimate the total development cost or deliver the product for a fixed price.

## *Extreme Programming (XP)*

### *Introduction*

Extreme Programming was developed starting in 1995 by Kent Beck, Ward Cunningham, and Ron Jeffries for a large application at Chrysler and later (1999) described in several books authored by Kent Beck, including "Extreme Programming Explained."[4,5]

### *Description of the Methodology*

The main items are:

- Many small iterations, built feature for feature.
- Priorities for functions are set for each iteration and are developed accordingly.
- Build each function as simple as possible; future enhancements are neither considered nor desired.

- The program always remains executable and allows quick feedback on the current program status.
- Changes and enhancements are possible at any time.
- In later development phases, a restructuring of the program code is often necessary.

The most important aspects of this methodology are - *Figure 2.*

- **Test-Driven Development**
  For every feature, which is developed, an automated test must be developed at the same time. Every function must be tested (100% test coverage) and the tests must be repeatable.

- **Permanent Integration**
  Every new function is integrated directly into the existing system – this creates a routine and minimizes the integration effort. Errors in the interaction between modules can be identified and resolved quickly.

- **Refactoring**
  The result of implementing "feature by feature" and always using the simplest solution results in a more-or-less unstructured code. Given the focus of XP on code quality and enabling the integration of new features, the existing code must often be restructured or redeveloped. All features remain testable thanks to the automated test procedures, which are developed alongside the code.

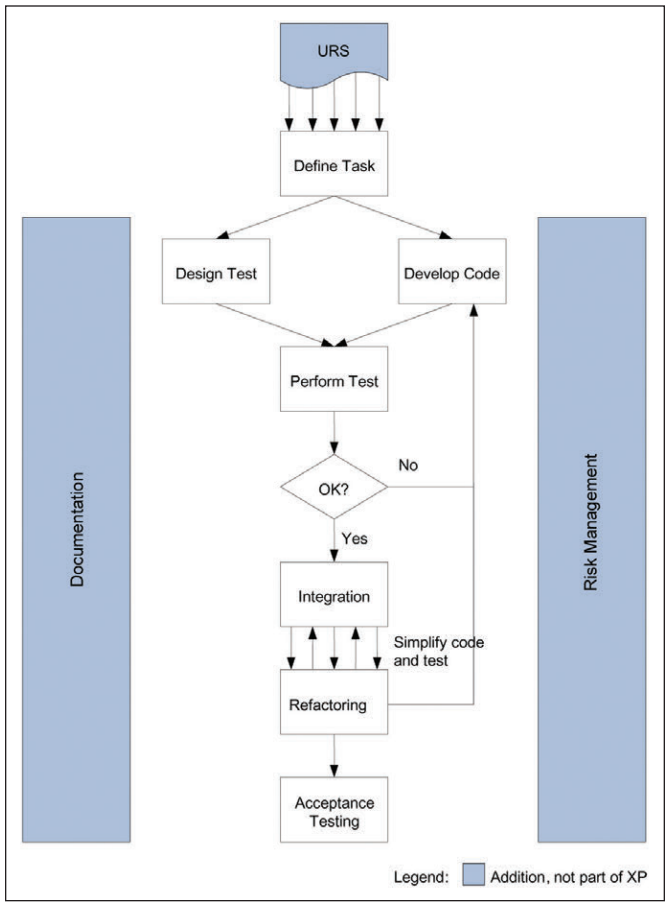


Figure 2. Extreme programming methodology.

| No. | GAMP 5 Development Document | Document Name or Activity | Comment |
|---|---|---|---|
| 1. | Requirements | Use Cases, User Stories | XP does not define any documentation method. The goal is a software which meets the needs of the customer and achieves a high level of quality through the "feature definition – develop test – develop code – integrate – improve code – perform regression testing" cycle. |
| 2. | Design | --- | |
| 3. | Implementation | Pair Programming, Code Review, Test-driven development, permanent integration | |
| 4. | Design Verification | Unit Tests, Function Tests, Regression Tests | |
| 5. | Requirements Verification | Customer testing of each iteration and release | |

Table C. Comparison XP – typical documentation.

- **Pair Programming**
  Two programmers (driver and partner) work together on one computer so that code is constantly reviewed interactively (four eyes principle). The roles are regularly reversed.

### *Applicability in GxP Environments*

Extreme programming sets standards for the creation and testing of software up to the acceptance testing by the customer - *Table C*. Further, XP defines rules to ensure the steady communication among the developers and the regular communication with the customer. It does not define standards for documenting the specifications or tests.

Extreme programming can be used in GxP environments when the required documentation is defined at the outset of the project and developed during the project life cycle.

For small to midsize projects, XP may be advantageous because the constant customer evaluation and feedback can ensure that the system meets their changing needs better than the rigid, sequential models. The intensive testing at all levels demanded by XP ensures that the final product has a high level of quality.

## *Iterative Conference Room Pilot (CRP)*

### *Introduction*

CRP uses the "rapid prototyping" methodology to develop or configure an application based on an existing software product, in order to transparently implement the user's requirements. The existing software product is modified or configured to meet the customer requirements in a series of iterative steps. Satisfying the customer needs and wishes is achieved through a quick, prototype-like demonstration of the requirements in the software. Detailed goals include:

- High coverage of the requirements through the application.

*Continued on page 20.*

- Quick feedback and evaluation of the features.
- Stepwise and quick convergence on the customer requirements.
- High level of understanding between the customer and the developer prevents misinterpretation and unnecessary efforts.

### *Description of the Methodology*

The CRP methodology[6] assumes that there is an existing software product available which can be used as a basis for implementing prototype-like configuration changes. Through a series of workshops and iterations, the software will be configured and/or customized. To achieve this goal, the following methodology is used:

- A rough requirements specification document exists and will be refined with the iterations (prototypes).
- A common practice is to use a 30-60-90 approach (whereas 30%, 60%, and 90% of the requirements are specified and implemented into the prototype).
- The CRP application is always available in a development environment.
- Changes and enhancements are possible at any time during the prototype phase.
- A list of functions meeting the user expectations (FIT list) and those requirements which are not yet satisfied (GAP list) is collected and maintained during the iterations. For each gap which has been identified, a System Change Request (SCR) is defined and managed.
- The list of gaps is reviewed and prioritized before each iteration and the changes are implemented according to these priorities.
- After the prototype has been approved, a "traditional" development methodology is used (later use of the prototype depends on reproducibility and documentation).

Figure 3 illustrates the overall iteration process.

### *Applicability in GxP Environments*

To enable a quick implementation, design documentation is often neglected or incomplete. The following lists are created and maintained during the CRP development:

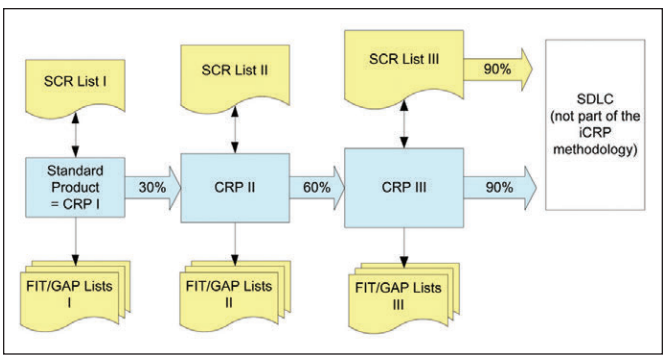


Figure 3. Method for the iterative convergence.

| No. | GAMP 5 Development Document | Document Name or Activity | Comment |
|---|---|---|---|
| 1. | Requirements | FIT/GAP lists<br>SCR lists<br>GAP list contains the risk priority | The CRP grows per the 30-60-90 principle, and is status-driven.<br>The closure/non-closure of a GAP must be justified. |
| 2. | Design | --- | --- |
| 3. | Implementation | --- | --- |
| 4. | Design Verification | --- | --- |
| 5. | Requirements Verification | Review of the implemented SCRs | For each completed SCR, the status is set to "accepted." |

Table D. Comparison CRP – typical documentation.

- The FIT list contains all of the functions (taken from the original software and configured as required), which already meet the requirements.
- The GAP list contains all gaps, which have been identified in the pilot phase. If this gap should be closed, the requirements will be specified more precisely and given a priority.
- System Change Requests (SCR list) – the selected changes from the gap list will be documented in a SCR list. This list grows with each meeting and documents the priority and the implementation status of each change.

The FIT and GAP lists identify and describe the functions and gaps in both the user requirements and application functions and can later be tracked in the form of SCRs. These lists replace the traditional requirements specification document and are referenced in the functional specification as changes to the standard (underlying) application.

When the CRP prototype has been completed, all subsequent development and test efforts should follow a traditional development methodology. Specifically, all of the documentation created (or not created) during the prototype and design phase must be reviewed and updated if not completely rewritten. The same holds true for the code developed during this phase – all code should be subject to a code review, and as applicable, corrected or redeveloped - *Table D.*

The system tests should be performed as described in the GAMP Guide. A detailed acceptance test may, under some circumstances, not be necessary.

## *Model Driven Architecture (MDA)*

### *Introduction*

Model Driven Architecture (MDA)[7] is a strategic initiative of the Object Management Group (OMG) to promote model-driven software generation and development. The OMG has created a vendor-independent specification to improve the interoperability and portability of software systems. MDA represents the use of models and generators to improve the development of software.

MDA pursues the goal to generate a sensible portion of the source code automatically. This may vary between 20 and 80 percent, depending upon the business process and requirements. Since the architecture of the system is implemented manually, this makes the MDA highly flexible and ensures complete control during the development process.

MDA describes a model-driven software development approach in which there is a clear differentiation between functionality and technology.

### *Description of the Methodology*

In MDA, the model becomes the central element of the software development process. A model may represent the architecture, functionality, or behavior of the system. In addition to the specification and documentation of the software, formal models are used to define the architecture, design, and implementation of the system. Models describe not only the static parts of a software module, but also the dynamic parts of the system.

The central concept of MDA is the separation of platform-independent and platform-specific models, each of which is independent of the other and is reusable. MDA breaks the overall model into several layers, as illustrated in Figure 4.

- The Computation Independent Model (CIM) is a (formalized natural language, e.g. UML) description of the requirements.
- The Platform Independent Model (PIM) describes (models) the business processes.
- The Platform Specific Model (PSM) describes (models) the architecture and system services.

The CIM represents the business or domain view of the required software system and is the model layer with the highest level of abstraction. The model is written in a language that is easily understood by the customer (key users) and serves as a discourse between the software architect and the customers to define their requirements for the system.

Through the PIM, the structure and behavior of the system is specified. This description is free of any technical aspects of the implementation and contains the components of the system, which can be described independently of the technical platform.

The PSM extends the PIM with technical details that are required for the implementation of the software system on a specific target platform, taking advantage of the technical interfaces provided by the platform. In addition to the division between the types of models, MDA also defines two types of transformation of the models:

- the transformation ("mapping") from one model layer into another model layer
- the transformation ("generation") from a model into program code

*Continued on page 22.*

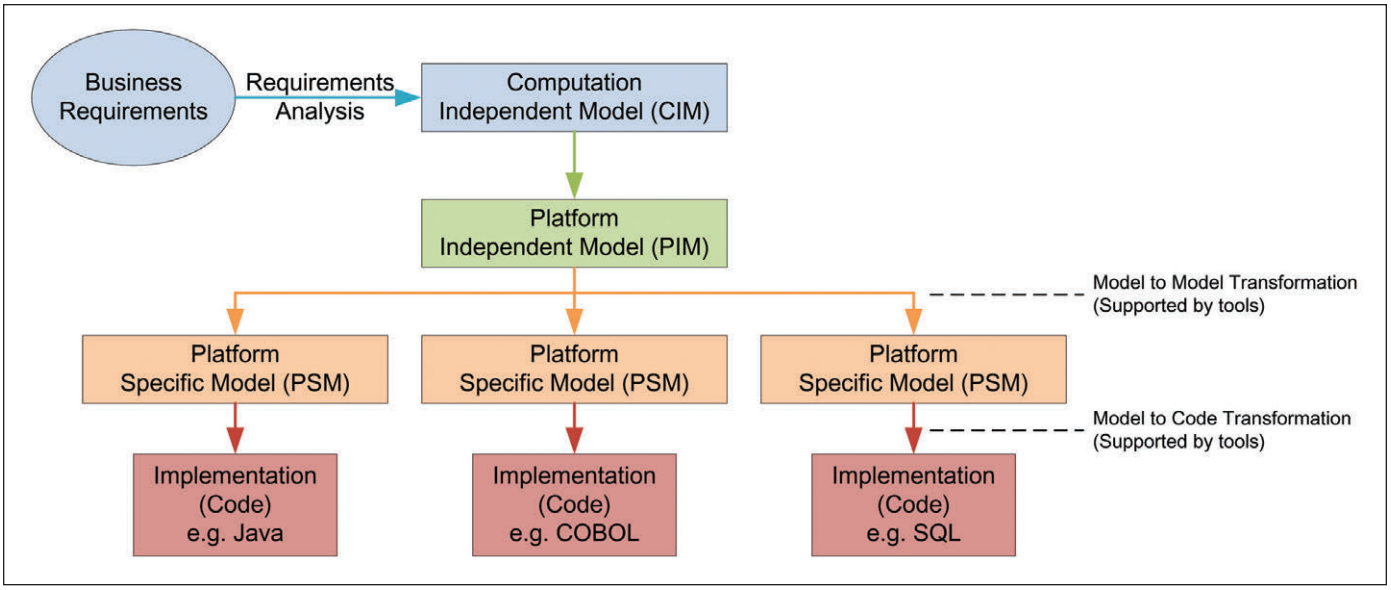


Figure 4. MDA concept.

Elements of the source model are transformed into elements of the target model. These transformations normally take place from the abstract layers to the concrete layers (CIM to PIM, PIM to PSM, and PSM to code). This way, simple model objects can be transformed into complex applications, when experienced software architects have programmed their construction rules into the transformation processes. The main emphases lie on the following aspects:

- easier to manage through a higher level of abstraction
- detailed, graphical specification of the requirements early in the process with automatically generated documentation through graphics and plans
- automatic "transformation" of the high level models and automated code generation

| No. | GAMP 5 Development Document | Document Name or Activity | Comment |
|---|---|---|---|
| 1. | Requirements | CIM | The scope of the GAMP Guide for a URS can only partially be satisfied. |
| 2. | Design | PIM, PSM | Complementary and combinations of both types of models is conceivable. |
| 3. | Implementation | Model to Code Transformation | Code is generated automatically by the software generator from the PSM models. Bug fixes and corrections are made to the generator, not in the code itself. |
| 4. | Design Verification | --- | Test specifications can be generated from the models. |
| 5. | Requirements Verification | --- | As part of the specification, the models can serve as the basis for test cases. |

Table E. Comparison MDA – typical document.

- easier adaption to new technologies (platform-independent)
- high level of consistence between the model and the program code
- definition of a test strategy based upon the selected hierarchy/structure used to build the models (e.g., define simulations)
- high reusability and longer useful life for the models including reduced maintenance effort

### *Applicability in GxP Environments*

The models should be seen as documentation since any change is implemented by changing the model or the transformation rules and the consistence of the documentation is ensured. The further use of MDA can lead to huge advances in the field of software development, whereby the focus is on the continued use throughout the product life cycle, where the documentation, simulators, and test applications are all produced from the modeling system. End-to-end, integrated solutions are in development or available from system vendors. The documents created during the MDA process (CIM, PIM, PSM) can be used as base of the validation documents required under GxP - *Table E*.

## Summary

The usefulness of the methodologies for validated systems can be summarized as follows:

### *Scrum*

The strength of Scrum lies in the disciplined approach to the project lifecycle, through an iterative questioning and revising of the requirements and their documentation. Requirements for the documentation of the design, implementation, testing, and acceptance are on the other hand, not specified by the scrum methodology. These phases must be executed and documented according to the GAMP Guide recommendations.

When the two central scrum documents, the product backlog and sprint backlog, are expanded to meet the GAMP 5 (attachment D1 and D2) recommendations, these should then represent GxP compliant URS and FS documents.

### *Extreme Programming (XP)*

The task definition, described as a series of use cases and user stories, can be iteratively developed into a complete URS, so that at the end of the project, a complete requirements analysis is available. The development tests (including 100% unit test coverage) are part of the methodology and are defined together with the requirements.

A design should be drafted, describing the system architecture and where/how each of the units is integrated into this architecture. Installation documentation is quite easy to create, as the deployment of competed components is constantly taking place.

The test documents (functional and acceptance tests) are defined in parallel with the development tasks, and with each iteration, these flow into the overall test pool. Here, the XP methodology supports not only the functional tests (in the form of regression tests for each iteration), but also the user acceptance tests.

### *Iterative Conference Room Pilot (CRP)*

The prerequisite for a CRP methodology is the existence of a suitable application, either in the form of a software product or a collection of reusable modules. Without this basis, the iterative development process cannot be started.

The user requirements are collected using the 30-60-90 approach and are evaluated in the FIT and GAP lists. At the end of the CRP phase, the FIT list describes all of the user requirements which will be included in the final product, and serves as the basis for the URS document.

A design should be drafted on the basis of the SCR list, describing the system architecture and where/how each of the units is integrated into this architecture. This is also necessary for the regular maintenance. The development tests can be derived from the SCR list as well.

### *Model Driven Architecture (MDA)*

The requirements from the CIM serve as the basis for the URS and describe the business process as well as the general requirements for the planned system, but this must be enhanced to satisfy the GAMP Guide recommendations.

The PIM and PSM model descriptions provide the basis of the design specification, which also must be enhanced to satisfy the GAMP Guide recommendations.

The MDA approach is optimal for an iterative-incremental methodology; it is in no way limited to or implies the use of a sequential methodology. The positioning of MDA in the software development process covers the analysis, requirements definition, design, and implementation – even the use during the test phases is conceivable, even though this is rarely done at the current time.

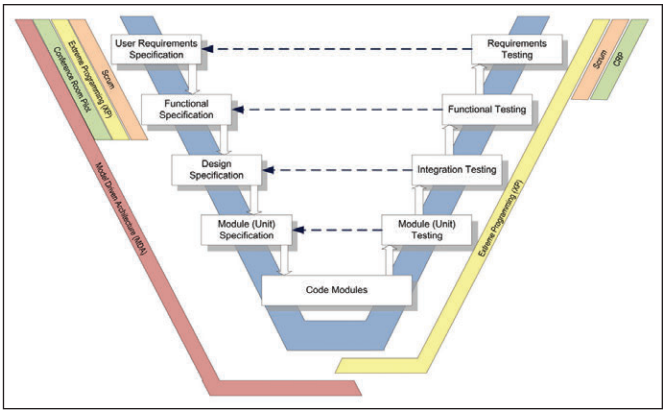


Figure 5. Mapping of the alternative methodologies to the V model timeline.

### *Mapping of the Methodologies to the V Model Lifecycle*

Figure 5 illustrates how the alternative development methodologies map to the implied timeline given by the V model whereas the respective specification must be frozen before testing can begin.

### *Evaluation of the Methods in Relation to GAMP 5*

The focus of this evaluation was to determine what documentation is produced as an inherent part of the selected methods

*Concludes on page 24.*

| | Lifecycle Documents | | | | |
|---|---|---|---|---|---|
| | Requirements | Design | Implementation | Design Verification | Requirements Verification |
| Scrum | 😐 Form Defined | ☹ Missing | ☹ Missing | ☹ Missing | 😐 Form Defined |
| Extreme Programming (XP) | 😐 Form Defined | ☹ Missing | ☺ Sophisticated | ☺ Automated | 😐 Form Defined |
| Iterative Conference Room Pilot (CRP) | ☺ Partially Functional | ☹ Missing | ☹ Missing | ☹ Missing | 😐 Form Defined |
| Model Driven Architecture (MDA) | 😐 Partial, machine-readable | 😐 Partial, machine-readable | ☺ Automated | ☹ Missing | ☹ Missing |

Table F. Overview.

and to analyze the gap to typical development documentation and transparency.

These gaps can be filled by applying documentation standards (e.g., GAMP 5) on existing information. These methods – even if the required documents are not all created inherently – can be used in the validation process. This information has been consolidated in Table F, represented with the following smilies:

☺ good consistency
😐 partially consistent
☹ not included or inconsistent

Table F further uses color and a few words to illustrate the evaluation results.

## Conclusion

The agile methods described in this document have evolved to provide the following features and benefits:

- using iterative steps to approach the desired solution
- real-time user testing of the implemented functionality
- control and discussion of the functionality directly in the application
- early and constant involvement of the user community
- flexible reaction to changing requirements and specifications
- avoiding the implementation of unnecessary functionality and code

From the description of the individual methodologies and the overview in Table F; it is clear that none of the discussed methods can on their own meet life science requirements for transparency of documentation.

As a consequence, one must conclude that additional efforts and activities (e.g., a comprehensive supplier QMS and regulated company compliance framework) are always needed to implement and maintain a GxP compliant validated system.

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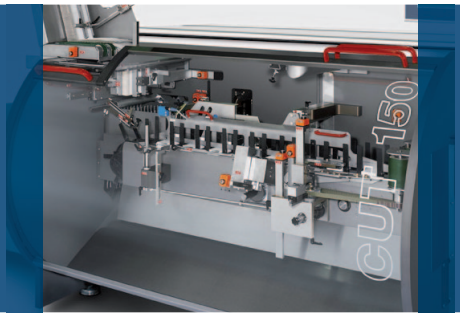


**This article presents a new type of risk tool. Risk Analysis and Mitigation Matrix (RAMM) was developed to be incorporated into a modern risk management system and align with latest FDA guidances.**

# Risk Analysis and Mitigation Matrix (RAMM) – A Risk Tool for Quality Management

by Alex Brindle, Steve Davy, David Tiffany and Chris Watts

Risk analysis and management is the cornerstone of any science- and risk-based approach[1] for modern drug development and manufacturing.[2] In order to understand and document processes and products, standard risk analysis tools have been adapted from other industries and academia. These tools include Ishikawa Diagrams,[3] P-Diagrams, Preliminary Hazard Analysis (PHA), Failure Modes and Effect Analysis (FMEA[4]), Failure Modes and Effect Criticality Analysis (FMECA[5]), Hazard Analysis of Critical Control Points (HACCP[6]), and several more.

The Risk Analysis and Mitigation Matrix (RAMM) was created to provide a pragmatic compromise where other risk tools such as Preliminary Hazard Analysis (PHA) or Failure Mode Effects and Criticality Analysis (FMECA) are maybe either too simple and lacking in detail, or they are maybe too complicated, making it difficult to work consistently with limited resource across all products.

The goal of the RAMM was also to align with ICH and FDA guidances (Q8 to Q10 series[7, 8, 9] and Process Validation[10]); especially around tracking Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) in a pragmatic manner. The tool was designed to be at the heart of any modern quality system with regular review in meetings and as a way of tracking risks and any mitigation actions. The tool had to be simple enough that everyone could use it and provide enough detail that critical risks could be tracked, mitigated, and be time savvy. If it were to take days to go through the risk analysis every time a process review occurred, it would never be as useable as it should be.

This article will discuss how the tool works, provide a practical example as applied to a monoclonal antibody (Mab) process, and show how to incorporate the tool into a quality management system.

## Use of Risk for Development and Manufacturing

When developing a new process and product or attempting to understand an existing process and product, knowing how materials, processes, and controls affect the final product is essential. If one can identify the critical process input factors, the variation in the process responses should be able to be understood and controlled. Without this knowledge, the developer or manufacturer is simply guessing how good products are made and most likely relying heavily on a quality control unit to reject any bad products manufactured.

From a development or manufacturing perspective, one of the key parts of this pathway is understanding which raw materials and process parameters impact the Critical Quality Attributes (CQAs). Furthermore, in what direction and quantity these parameters affect the CQAs are critical for manufacturing excellence. This is because this understanding can be used to develop more robust processes or add appropriate control measures to adjust processes to make on target product.

## Risk Hierarchy

Risk tools are traditionally categorized as simple or detailed. Simple tools are often used as a precursor to using the detailed tools or early in development where little is known about processes, materials, and products. These simple tools include:

*Continued on page 28.*

**My people are forced to waste their time on monotonous procedural tasks. I need them focused on right-first-time production instead.**

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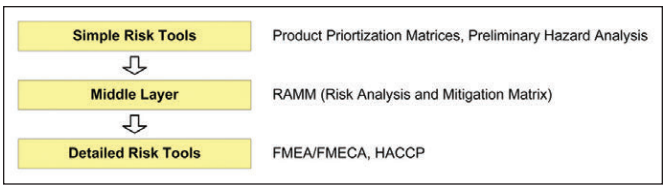


Figure 1. Risk hierarchy and introduction of middle risk layer tool.

- Ishikawa Diagrams
- Preliminary Hazard Analysis (PHA)
- Simple Prioritization Matrices
- P-Diagrams

The list above is not exhaustive and the output of simple risk tools are not particularly quantitative and are typically for identification or hazards and/or risks only. These tools are extremely simple to use and yield results quickly.

More detailed tools are used for comprehensive risk analysis (and mitigation steps) and include a quantitative element. Examples of these tools include:

- Failure Modes and Effects Analysis (FMEA)
- Failure Modes, Effects and Criticality Analysis (FMECA)
- Hazard Analysis and Critical Control Points (HACCP)

The use of these tools typically leads to a comprehensive analysis of risk. All of these risk tools, either simple or detailed, could be complimented by a middle level risk tool as demonstrated in Figure 1. The Risk Analysis and Mitigation Matrix (RAMM) was developed to be quantitative yet simple to use.

The RAMM tool is potentially a useful compliment to the other risk tools and can be used solely or in combination with other risk tools. The potential to use something quantitative, but not as complex as the detailed risk tools can potentially serve as the useful keystone of a risk management system as it is quantitative yet manageable. Each user should of course make their own choice as to which tools serve them best, but it is proposed that the RAMM is a useful addition to that tool set.

## Use of RAMM Tool for Monoclonal Antibody Process

The RAMM tool was applied to an example monoclonal antibody process. The tool was applied in six stages as part of a risk management system.

### *Stage 1 – Team Formation*

The first step was selecting the right team to be involved with the RAMM workshop sessions. This situation dealt with an example of a product in late stage development; therefore, the following functions were selected to be involved in the workshops:

- Process Development
- Product Development
- Analytical Development
- Manufacturing
- Quality
- Regulatory
- Medical Professional
- Facilitator

It was felt that this team would give the best input to developing the process understanding and risk analysis, although each organization and project is different and may include different functions to those selected here. Though it was not the case in this example, the "right team" may include people who have not seen the actual process before, but who have other experiences. It is important that these individuals get an opportunity to "walk the process" so they get an understanding of what they are dealing with in terms of how the process is run on a daily basis.

### *Stage 2 – Identifying the CQAs*

The strict regulatory definition would be related to CQAs related to strength, purity, and efficacy. The interpretation of CQAs can mean different things to different organizations. In this example, Quality and Regulatory had already defined what this should be as the team was well into preparation for submission documentation. These CQA definitions were developed as an interpretation of pragmatic representation of desired CQAs and what was practicably measurable and easily understood with no risk of confusion. The CQAs were defined as the following:

- Mycoplasma
- Viral Contamination
- Identity
- Acidic Variable Levels
- Yield
- Concentration Assay
- Purity Assay
- Visual Appearance
- Osmolality
- pH
- Residual Host Cell Protein
- Residual Host Cell DNA
- Bioburden
- Endotoxin
- Viral Clearance

These CQAs would make up the header row of the RAMM analysis.

### *Stage 3 – Define the Process Steps*

The process steps are considered the major contributors that cause the starting material to be converted to final product. Although this seems complex at first, a great many processes use very similar process steps.

The next piece of pre-work involved process development and manufacturing to prepare the actual process, which would be the center point of the RAMM. This process was defined

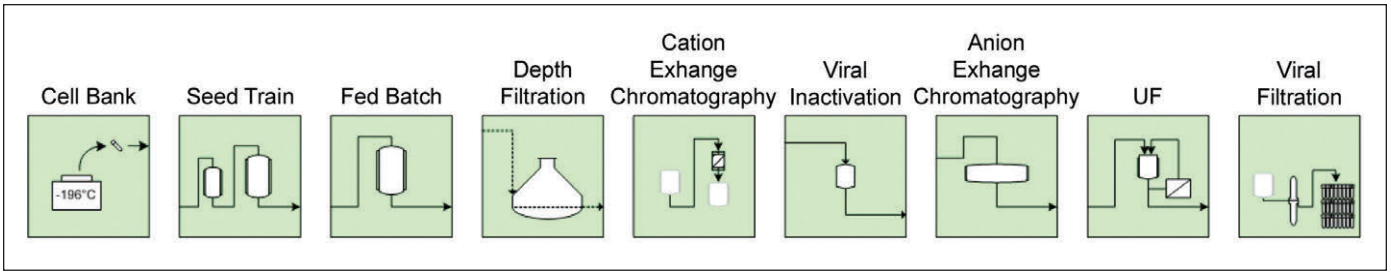


Figure 2. Monoclonal antibody described as process block diagram.

in its current state, it was understood the development is an iterative process, and the process tomorrow may be different from that of today. For this example, the process is a fairly straightforward Mab process utilizing single use technology for several of the process steps (in addition to media production).

Production of the monoclonal antibodies was in a fed-batch culture using a single-use bioreactor. The harvest was then clarified by depth filtration using single-use pods. Cation-chromatography was used for a capture-hold step with a reusable column. The product was then transferred to a single-use bag in a mixing tank at which point low pH was used to deactivate the virus for 40 minutes. The product was then polished by membrane filtration (anion-exchange). The product yielded from the anion exchange chromatography, and the yield was calculated by assay. The product was then sent to single-use ultra-filtration apparatus for buffer exchange. Using the ultra-filtration apparatus, the product was initially concentrated. The concentrated volume was then exchanged by diafiltration into a volume of formulation buffer, determined by the yield calculated by assay following the anion-exchange chromatography. These steps are shown in Figure 2.

### *Stage 4 – Define Process and Material*

Once the overall process is defined, each process step should be broken down into process parameters (some of which would become critical process parameters) and other important parameters.

A P-Diagram was used to capture process parameters in this example; an example can be seen in Figure 3. Each process block is analyzed to determine which inputs, or factors, to that process step are present. These are depicted with an arrow pointing toward the box identifying the process step. Process responses or outputs are depicted with an arrow pointing away from the process step.

Outputs contributing to the next interim step in the process can be shown with the arrow pointing to the next step, but as all outputs do not contribute directly to the next process step, this may be confusing. In practice, the process outputs are generally shown simply pointing away from each process step.

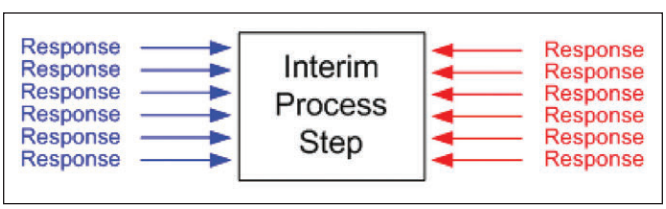


Figure 3. P-diagram showing process inputs and process outputs.

In this example, the P-Diagram was felt to be the most useful, but other simple identification risk tools could have been appropriate such as an Ishikawa Diagram. In this instance, the team felt that systemic issues where well documented around materials and human effects and wanted to concentrate on process parameters.

In addition to the P-Diagram, material attributes also where identified and listed along with systemic issues such as staff training and equipment setup.

### *Stage 5 – Create RAMM and Score It*

The RAMM uses a matrix of process input factors and quality attributes to assess risk and impact. Now that the critical quality attributes and process (or material or other) parameters have been defined, the matrix of these two axes forms the basis of the RAMM. The top row of the RAMM is used to document important responses or quality attributes, and the left most columns are used to describe process steps and process inputs (including material and other parameters).

Once each process step is depicted, the inputs for process parameters can be transferred from Stage 4 (the P-Diagram or other similar tool) to the input column on the RAMM document. It is recommended that the process step be identified as well, in a separate column to the left, as multiple process steps may have similar inputs (consider temperatures, speeds, pressures, etc.).

Assigning stratified scores (one for factors having low impact or risk, three for factors having moderate impact or risk, and nine for factors perceived as having high impact or risk) also facilitates identification of the important factors, and greatly speeds the process. Experience shows that if a group has ten choices to choose from (one to ten), they will become increasingly concerned with the small difference between the scores; for example, "Is it a five or a six?" The stratified (and limited) choices make the decision easier and faster: the important risks or parameters really are important and deserve a high score. The unimportant risks or parameters can receive a low score. The items in between can be assigned a moderate score.

Why are moderate items not scored a middle value, like five? One of the objectives of the RAMM is to force the user to consider the really important items. By weighting the important items, they are elevated to the top and demand

*Continued on page 30.*

| 9 | 9 | 9 | 9 | 3 | 3 | 9 | 1 | 1 | 1 | 3 | 9 | 9 | 9 | 9 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mycoplasma | Vial Contamination | Identity | Acidic Variant Levels | Yield | Concentration (UV Assay) | Purity Assay (HPLC) | Visual Appearance | Osmolality | pH | Purity | Residual Host Cell Protein | Residual Host Cell DNA | Bioburden | Endotoxin | Viral Clearance |

Table A. CQAs and relative criticality.

attention. This weighting will help prioritize the study of issues and drive mitigation actions.

To quantitatively assign the relevant importance of the CQAs, a relative priority score of one, three, or nine (one being relatively important and nine being critical) was assigned. This was greatly assisted by a medical professional (called into the workshops by telemeet on this occasion) to accurately score the CQAs by relating them back to importance to the patient.

With the CQAs defined and ranked (as highlighted in Table A), the process and material piece was analyzed in depth to break down each process unit into individual process parameters. The cross-functional team scored the risk or impact of each parameter or other parameter with relation to each CQA. Scores are limited to stratified levels of one (minor), three (moderate), and nine (high). Stratifying the scores reduces the time required to complete the analysis, while still assessing the relative importance of each factor.

Additionally, parameters which affected the product outcome, but were not necessarily process step specific, also were analyzed. This included items such as raw material properties and their subsequent scoring to critical material attributes.

The example shown in Figure 4 includes only a fraction of the process steps analyzed (this shows details for just one process step) in order to logically fit this report into this article.

In this example, a parameter was defined as critical if it had a direct impact on a CQA. The team discussed what would require action and follow-up work to improve the criticality. The end definition was any process parameter that flagged red (or critical) for a CQA that was also ranked as critical. In addition, the total risk score (similar to a risk priority number) was also used as a flag for anything with a total score of 200 and above, and would require immediate action plans. This definition of 200 and above was a team decision about what was the justified total risk score at which action should be taken based on their knowledge of the product, science, patients, processes, and materials.

At this stage the RAMM could be sorted and filtered so that process inputs can be assessed by their impact on a specific response, by the interim process step, or for their overall impact on the entire process. Likewise, the matrix could be filtered to determine which process step or input factor(s) had the greatest impact on a particular attribute. The order of cross products for both the rows and columns were "gut-checked" with the cross-functional team to ensure the scoring agrees with their perceptions of the process. The parameters receiving the highest cross product scores were checked that they aligned with the cross functional team's consensus of most important or highest risk parameters.

It can be seen above that for the process step highlighted and the defined criticality flagging criteria that there were several criticality points requiring further action. These included:

- N-1 stage cell expansion – equipment setup
- N-1 stage cell expansion – temperature control
- N-1 stage cell expansion – agitation
- N-1 stage cell expansion – dissolved oxygen
- N-1 stage cell expansion – post inoculation temperature

### *Step 6 – Mitigation*

The final point of discussion of the workshop was to assist in defining which action would help mitigate risk for these process parameters. The key action defined was around gaining improved process robustness. In order to improve this, experiments were defined. Additionally, it was indicated that some changes to the equipment would improve the equipment setup weaknesses.

At this point, the team was adjourned, any documents

| Relative Importance of CQA → | | | 9 | 9 | 9 | 9 | 3 | 3 | 9 | 1 | 1 | 1 | 3 | 9 | 9 | 9 | 9 | 9 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Monoclonal Antibody | | | Mycoplasma | Viral Contamination | Identity | Acidic variant levels | Yield | Concentration (UV Assay) | Purity assay (HPLC) | Visual Appreearance | Osmolality | pH | Purity | Residual Host cell protein | Residual Host Cell DNA | Bioburdin | Endotoxin | Viral clearance | Total |
| Process Step | Class | Process Parameters or Material Attribute | | | | | | | | | | | | | | | | | |
| N-1 stage cell expansion | Personnel | Equipment setup | 3 | 3 | 1 | 3 | 3 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 9 | 3 | 1 | 276 |
| N-1 stage cell expansion | Method | Batch media volume | 1 | 1 | 1 | 3 | 3 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 150 |
| N-1 stage cell expansion | Method | Temperature control | 1 | 1 | 1 | 9 | 9 | 9 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 240 |
| N-1 stage cell expansion | Method | Agitation | 1 | 1 | 1 | 9 | 3 | 9 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 210 |
| N-1 stage cell expansion | Method | Dissolved Oxygen | 1 | 1 | 1 | 9 | 9 | 9 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 240 |
| N-1 stage cell expansion | Method | Overlay CO2 flow rate | 1 | 1 | 1 | 3 | 3 | 3 | 1 | 1 | 1 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 146 |
| N-1 stage cell expansion | Method | Overlay air flow rate | 1 | 1 | 1 | 1 | 3 | 1 | 1 | 1 | 1 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 128 |
| N-1 stage cell expansion | Method | Sparge air flow rate | 1 | 1 | 1 | 3 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 132 |
| N-1 stage cell expansion | Method | Post-inoculation temperature | 1 | 1 | 1 | 9 | 3 | 9 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 210 |
| N-1 stage cell expansion | Method | Culture duration | 1 | 1 | 1 | 3 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 132 |

Figure 4. Process parameters with CQAs with risk scores detailed for just one process step (N-1 cell expansion).

| Relative Importance of CQA → | | | 9 | 9 | 9 | 9 | 3 | 3 | 9 | 1 | 1 | 1 | 3 | 9 | 9 | 9 | 9 | 9 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Monoclonal Antibody | | | Mycoplasma | Viral Contamination | Identity | Acidic variant levels | Yield | Concentration (UV Assay) | Purity assay (HPLC) | Visual Appearance | Osmolality | pH | Purity | Residual Host cell protein | Residual Host Cell DNA | Bioburdin | Endotoxin | Viral clearance | Total |
| Process Step | Class | Process Parameters or Material Attribute | | | | | | | | | | | | | | | | | |
| N-1 stage cell expansion | Personnel | Equipment setup | 3 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 1 | 174 |
| N-1 stage cell expansion | Method | Batch media volume | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 120 |
| N-1 stage cell expansion | Method | Temperature control | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 120 |
| N-1 stage cell expansion | Method | Agitation | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 108 |
| N-1 stage cell expansion | Method | Dissolved Oxygen | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 120 |
| N-1 stage cell expansion | Method | Overlay CO2 flow rate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 114 |
| N-1 stage cell expansion | Method | Overlay air flow rate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 120 |
| N-1 stage cell expansion | Method | Sparge air flow rate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 108 |
| N-1 stage cell expansion | Method | Post-inoculation temperature | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 108 |
| N-1 stage cell expansion | Method | Culture duration | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 108 |

Figure 5. Process parameters with CQAs with risk scores detailed for process step (N-1 cell expansion) (after one round of mitigation actions).

signed and workshop team members documented. The RAMM was incorporated into the quality system and a meeting set up for two months later to follow up on how the suggested improvement projects had mitigated risk.

The suggested action steps worked convincingly, greatly improving process understanding and reducing risk for this process step. No further action were deemed necessary at this stage for this process step to lower risk, as it was considered under control and well understood. The RAMM was updated accordingly to demonstrate that risk has been reduced changing the risk scores and providing a simple signal that risk had changed from reds and yellows to greens. This can be seen in Figure 5. It should be noted that other process steps were more complex to understand and required several rounds of mitigation actions to mitigate risk to an acceptable level.

Figure 6 shows that good overview can be gotten at the macro level showing overall risk for a product. This can be especially useful in trying to gain overview at a glance of the risk and how mitigation is working.

A RAMM typically takes one to two days to perform the first time with a team that has some knowledge of the process. This time can be significantly reduced for subsequent products especially if process steps and products are somewhat similar.

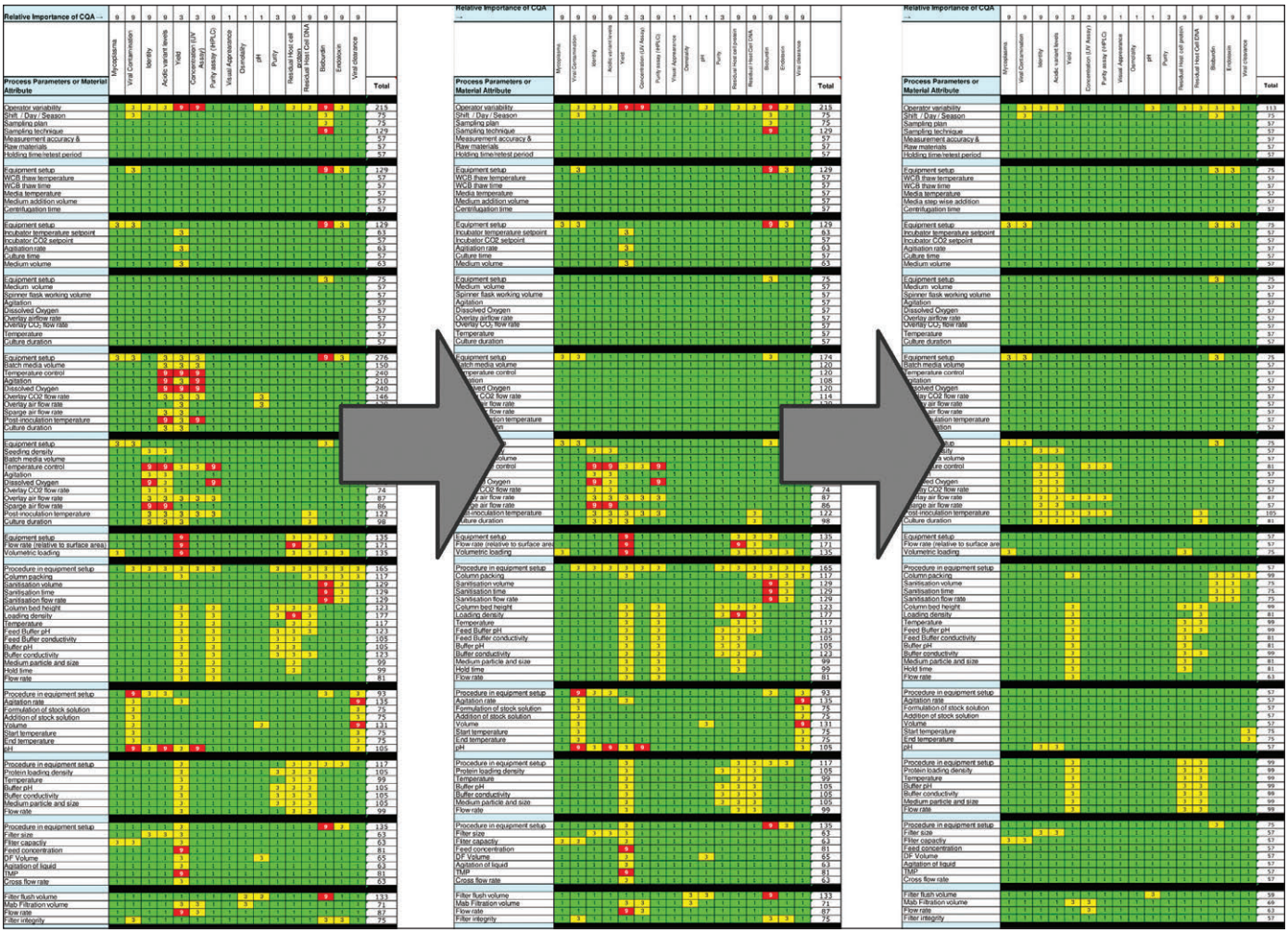

Figure 6. Impact of mitigation actions on total process and material risks. Mitigation actions change the risk flags from red to yellow or green.

*Continued on page 32.*

## Incorporation of the RAMM into the Quality System

The RAMM can be an integral part of an effective quality management system, facilitating implementation of the enabling concepts, knowledge management and quality risk management. This has been elucidated in the Guidance for Industry, ICH Q10 Pharmaceutical Quality System.[11] Inclusion of such a tool in corporate policies/procedures documents the approach to quality risk management, formalizing the systems for assessing, controlling, communicating, and reviewing risk to product quality. Additionally, use of such a tool offers a logical method for continually acquiring, analyzing, storing, and communicating information related to a specific product and its manufacturing processes.

One approach to integrating the RAMM into a quality management system would be to include the RAMM as a tool to be used in a process validation program. The example in Figure 7 demonstrates a quality system hierarchy with the Process Validation Guidance[12] fully incorporated through Process Design (stage 1), Process Qualification (Stage 2), and Continued Process Verification (Stage 3). Policies and/or procedures for the process development may describe the RAMM as a deliverable of Stage 1 of Process Validation. As knowledge is gained throughout the product/process lifecycle (i.e., through Stages 2 and 3 of Process Validation), the RAMM would be reviewed and updated accordingly in order to document the understanding (or lack thereof) and justification for reducing (or increasing) the risk attributed to each step of the manufacturing process. Such a practice would not only track the history of the process development and maintenance, but also document the development of the control strategy and any associated process improvements.

As previously described, the RAMM conveniently maps quality attributes against process parameters (the risk to product quality associated with each step of the manufacturing process). This practice then provides a proactive means to identify and control risks to product quality throughout the product lifecycle from development to routine commercial manufacture and product discontinuation. Effective and consistent risk-based decisions regarding product quality are thus enabled (by both regulators and the regulated industry), allowing an objective means to allocate appropriate resources to address unacceptable risks.

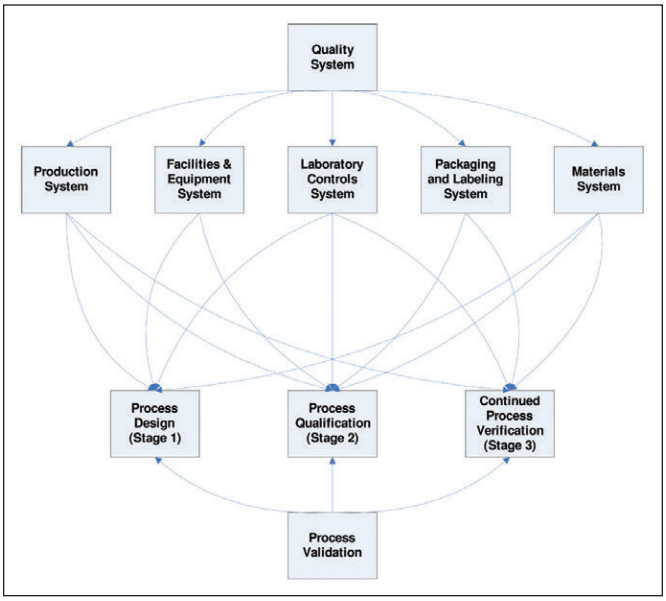


Figure 7. Quality system hierarchy.

The RAMM offers a systematic approach to quality risk management, providing a sound, risk-based foundation to a corporate QMS. Although relatively simple in structure, the RAMM is a comprehensive tool that complements existing quality practices, standards, regulatory requirements, and recommendations. Furthermore, as an effective mechanism for quality risk management, the RAMM facilitates better and more informed decisions, which may provide regulators with greater assurance of a company's ability to identify and address potential risks to product quality.

## Conclusion

The RAMM offers a risk analysis tool that may prove useful to some as the cornerstone of a quality management system. The authors have found RAMM extremely useful for risk management for various reasons and these include:

- The RAMM neatly handles CQA and CPP (including material attributes and others) parameters in one document and is easily aligned with latest guidances.
- The RAMM is fast; by presenting in a matrix that overlays CQAs against CPPs (including material attributes and others), it is relatively straightforward to set up and rank.
- The RAMM has speed, but is also relatively detailed allowing risk quantification or other risk flags to be identified in detail.
- The RAMM gives excellent overview – an entire process can be printed on just one to two sheets, allowing the overall process to be very easily explained with detail.
- The RAMM is very easy to incorporate into a quality system, follow up on, and make documented changes with.

The authors also have noted some disadvantages to the RAMM:

- The team using RAMM needs to be aligned and have some knowledge of risk analysis; this is especially true of scoring numbers as the individual risks are a combination probability and impact.
- If the process is not well understood, the team needs the experience to realize that some pre-work identifying parameters (such as p-diagrams) are required.

All in all, all risk tools have their value in a risk management system. It is expected that tools like RAMM will be especially

useful for organizations with large numbers of products where the application of detailed analysis tools to every single process and product would not be feasible. Here the RAMM could be used as a total replacement for detailed risk tools or act as a middle risk layer to prioritize which products and processes should have detailed risk analysis applied.

## Notes

The RAMM template is available as free templates and downloadable examples. Please contact the creators Alex Brindle and David Tiffany for details. The development and testing of RAMM was greatly helped by the following individuals: Line Lundsberg-Nielsen, Lene Bjerregaard, and George Kizhakethil.

## Acronyms

| | |
|---|---|
| CMA | Critical Material Attribute |
| CPP | Critical Process Parameter |
| CQA | Critical Quality Attribute |
| FDA | Food and Drug Administration |
| FMEA | Failure Modes Effect Analysis |
| FMECA | Failure Mode and Effect Criticality Analysis |
| ICH | International Conference on Harmonization |
| PHA | Preliminary Hazard Analysis |
| RAMM | Risk Analysis and Mitigation Matrix |

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**This article presents the current limitations of outdated sample preparation workflows in analytical R&D and QA/QC laboratories and introduces new approaches to improving quality and reducing variability, errors, and Out-of-Specification (OOS) results.**

# Reducing Variability and Out-of-Specification Results by Implementing High Quality Gravimetric Sample Preparation (GSP)

by Klaus Fritsch, Joanne Ratcliff, and Charles Ray

Out-of-Specification (OOS) results have had a significant impact in the pharmaceutical industry for many years, but especially since the Barr Labs court ruling in 1993.[1] In this case, the court ruled in favor of Barr Labs which upheld their view that an OOS result does not necessarily constitute a batch failure, but it should be investigated to determine if there are other causes such as a laboratory error. However, the court did not like the way Barr Labs was conducting their laboratory investigations. Since this ruling, the FDA revamped their guidance in October 2006 concerning how to handle OOS results and how to perform a proper investigation.[2] Since then, the FDA has issued a significant number of 483 observations concerning poor investigations.

A recent three-part article concerning OOS investigations by Lanese[3] begins by saying:

*"Out-of-specification. It's a term that brings the fear of the gods to the laboratory. It causes gridlock, finger pointing, and delays in the normal workflow."*

It seems that even five years after the guidance and 18 years after the Barr ruling, there is still a lot of work to do in this area.

Furthermore, in the FDA guidance concerning OOS investigations,[2] the FDA states that:

*"Laboratory errors should be relatively rare. Frequent errors suggest a problem that might be due to inadequate training of analysts, poorly maintained or improperly calibrated equipment, or careless work."*

Since the FDA is still issuing a significant number of 483 observations on poor investigations, the incidence of laboratory errors may not be as rare as we would like. Unfortunately, there is no published data which shows that for every OOS result generated, there were many more minor errors that didn't lead to an OOS result. These errors may have been classified as a "Note to Record," or simply noted in the laboratory notebook as an error. Many companies don't investigate these errors even though they are probably symptoms of potentially more serious issues with the analysis method or process.

In this article, the discussion will demonstrate how the current volumetric approach can cause OOS results and how those OOS results can be avoided by implementing a gravimetric system. The pitfalls of using a volumetric method will be explained by examining a simple sample preparation workflow, including specific examples of where errors and inefficiencies are introduced using the volumetric system. A review of good weighing practices is presented as the principle on which the revolutionary gravimetric approach to sample preparation is based. This gravimetric system, which involves automated weighing and dispensing of the solid and of the solvent, will reduce laboratory errors and increase laboratory efficiency.

To begin, let's look at how we spend our time and where the errors come from. An article was published about 10 years ago in *LC/GC Magazine* concerning OOS results.[4] The article

*Continued on page 38.*

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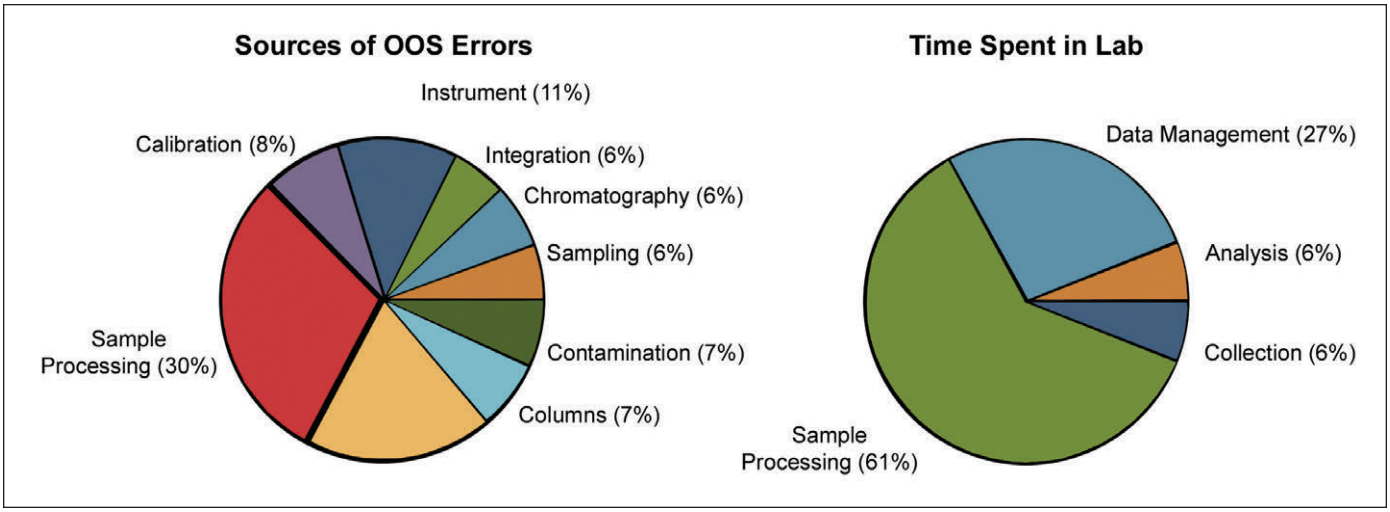


Figure 1. Sources of OOS results and time spent in lab.

discussed two aspects of laboratory work: first, what errors cause OOS results and second, the Full Time Equivalent (FTE) spend in the laboratory. This survey indicated that the two largest sources of OOS results come from human error and sample processing - *Figure 1*. Even though there has not been a follow-up survey since, from our work experience and from many discussions with colleagues and peers, it appears that this survey is true today and maybe even more so than 10 years ago. Our instrumentation, data systems, and columns have improved significantly during the last 10 years, but our sample processing has remained essentially the same. Since these other improvements have resulted in reduced time spent on them, the sample processing aspect of the laboratory work is probably now even greater than 61% of our FTE.

This article does not discuss how to investigate OOS results. Figure 2 is an example of a simplified workflow process for investigating an OOS result. There is a lot of effort expended when a sample has an OOS result and there have been numerous articles published on how this process should work. Obvious OOS results may take three days of work and serious ones may take months of work. The cost can easily run into many thousands or tens of thousands of dollars. Regardless of the amount of information that is published, it still seems to be a mystery to many companies and it is an especially difficult concept for companies in India and China to understand. Given the large impact that an OOS result has on the company, the best course of action should be to put every effort into avoiding them in the first place.

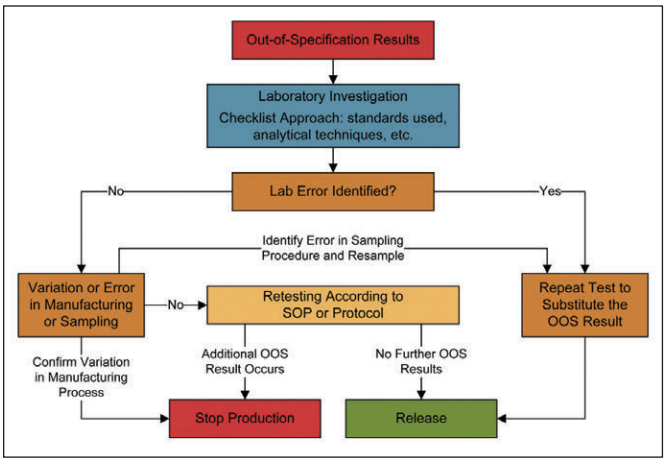


Figure 2. Formal process for an OOS investigation.

Besides trying to determine the root cause, the other significant issue seems to be the mounting Corrective and Preventative Actions (CAPAs) that the company may generate over a number of years that are the result of these laboratory investigations. These CAPAs typically cause procedural changes to SOPs and other documents and over time they become unmanageable and difficult to follow which causes even more issues.

The overriding problem with CAPAs is that, in the vast majority of cases, it is assumed that it is an isolated incident and address only a specific item in a workflow or process. In other cases, there is a tendency to blame a single employee or a simple laboratory error. In some cases, this simple error may be the only thing that needs to be fixed, but in many, if not most cases, the process or workflow should be fixed and not just this one item. This is especially true of sample preparations in the laboratory.

## Types of Laboratory Variability (Errors)

To be able to deal with variability in the laboratory, what types of variability there are and where they occur must first be understood. Variability in the data generated comes from two sources, determinate and indeterminate errors. A determinate error has a definite direction and magnitude and has an assignable cause; their cause can be determined. Determinate error is also called systematic error. Determinate errors can (theoretically) be eliminated through instrument adjustments. Indeterminate errors are also called random errors or noise. Indeterminate errors can be minimized, but cannot be eliminated. Some examples of these types of errors can be found in Table A.

## Sample Processing Steps

The largest cause of indeterminate errors in the laboratory

*Continued on page 40.*

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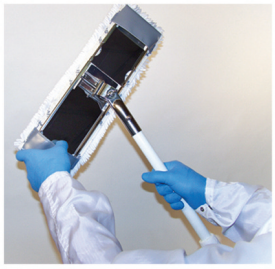

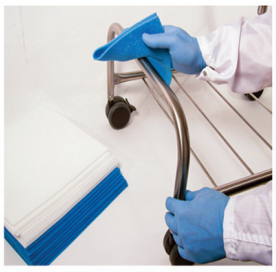

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| Step | Volumetric | Gravimetric |
|---|---|---|
| 200 mL container | DE = 0.05%<br>IE = un-calibrated | NA |
| Weigh 50 mg sample | IE = 0.1% balance<br>IE = others are accounted for using a safety factor of 2 | IE = 0.1% balance<br>IE = others are accounted for using a safety factor 1.5, if automated. |
| Sample transfer | DE = re-weighing weigh container<br>IE = powder transfer | NA |
| Fill to mark | IE = reading meniscus and temperature effects | NA |
| DE = Determinate Errors, IE = Interdeterminate Errors | | |

Table A. Comparing volumetric and gravimetric processes.

is from manual operations where the human factor comes into play. As shown in Figures 1 and 2, sample processing and human operations are the biggest source of laboratory errors. To understand why this is the case, let's take a look at a simple sample preparation and see what might be involved and identify where the problems and issues are.

Figure 3 shows the process for a simple sample preparation. The steps are grouped into four areas. The first one concerns gathering materials and ensuring the equipment is clean and calibrated. There are a number of steps at the beginning that may not result in an OOS, but would show up in both GxP and safety audits. Resolving these audit issues

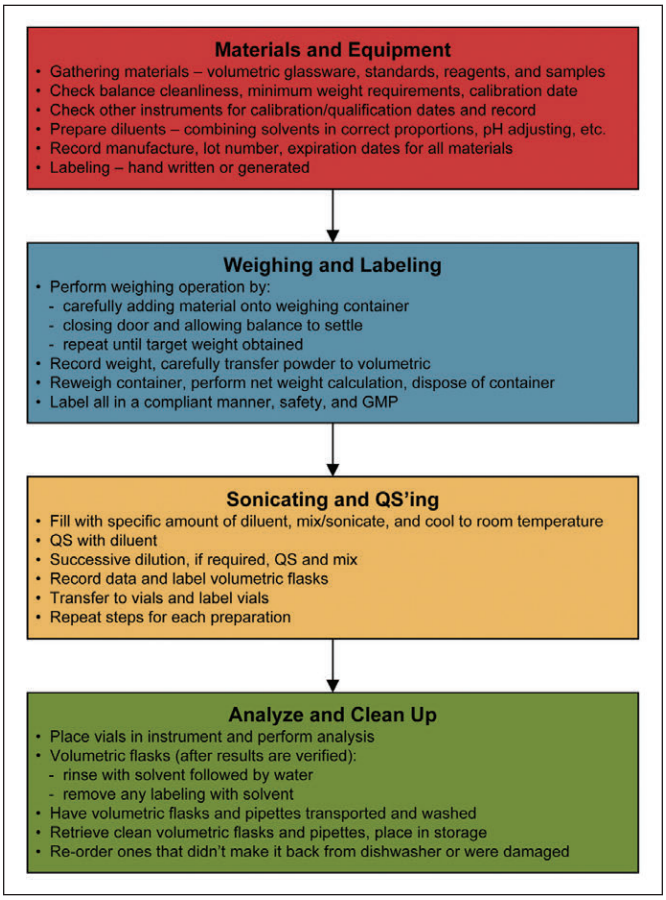


Figure 3. Simple sample prep workflow.

takes a significant amount of time and effort and also should be avoided since they may cause future OOS results.

The next area involves weighing and labeling. These are time consuming operations and the weighing steps can contribute to OOS results, but since this step is manually intensive, it can potentially make it difficult to determine the root cause of this operation.

Following weighing, there is adding the diluent, sonicating, QS'ing, and any successive dilution that may be required. The weighing, sonication, and QS'ing steps are repeated for each standard and sample.

Finally, the samples are analyzed and the materials and equipment are tidied up. This involves disposing of unused solutions, rinsing flasks and pipettes, and other resupply steps.

Therefore, a simple process takes about 10 or more steps and there are another 10 or so miscellaneous steps. If two standards and a sample were to be prepared, approximately 40 steps would be performed. A 40 step process has a significant number of areas where problems can occur at any time. Furthermore, some of these steps can be expanded and a detailed analysis might result in even more steps. If more complicated operations like extraction and filtering were to be included, the number of steps could reach 100 or more. Given this number of manual steps where indeterminate errors occur, some might wonder why we don't have even more OOS results. Fortunately, many but not all of these errors are found before the final results are obtained, but they do significantly impact the productivity of the laboratory operation and the overall quality of the data.

## Sample Weighing – Good Weighing Practices for the Pharmaceutical Industry

Weighing is a key activity in most laboratories, but it isn't always sufficiently understood and its complexity is often underestimated. As the quality of weighing strongly influences the quality of the whole sample and standard preparation process, USP specifically requires in its General Chapter <41> highly accurate weighing results used for quantitative analysis.[5]

*"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 […] does not exceed 0.1% of the reading. Measurement uncertainty is satisfactory if three times the standard deviation of not less than ten replicate weighings divided by the amount weighed, does not exceed 0.001."*

Such a stringent requirement is not implemented for other instruments, where quite often the analytical development group sets the method requirements.

State-of-the-art strategies for adhering to consistently accurate and reliable weighing processes comprise scientific methodologies on balance selection and testing.[6] Within these methodologies, typical misconceptions on weighing which are very widespread in the industry are also described.

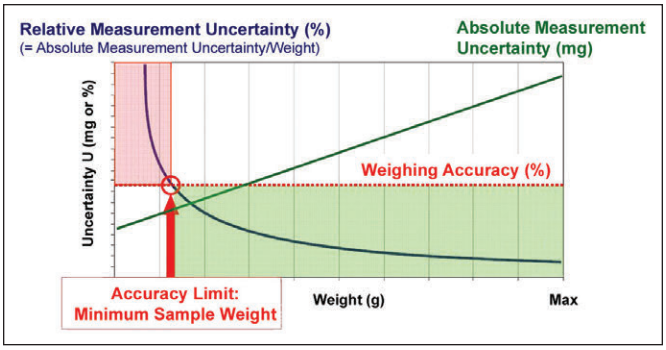


Figure 4. Measurement uncertainty: absolute (green line) and relative (blue line) measurement uncertainty of a weighing instrument. The accuracy limit of the balance, the so-called minimum weight, is the intersection point between relative measurement uncertainty and the required weighing accuracy.

One of them is that many users believe "what you see is what you get." What do we mean by that? Here's an example: a user weighs a standard on a semi-micro balance and gets a reading of 50.13 mg which he believes is the true amount of material that he was weighing. However, this reading might not exactly reflect the amount weighed, in other words, the amount weighed might differ slightly from the indication. This is due to the so-called measurement uncertainty which is inherent for every instrument you might think of.

Measurement uncertainty of instruments is determined in calibration, and the results issued in appropriate calibration certificates. In general, measurement uncertainty of weighing systems can be approximated by a straight line – the higher the load on the balance, the larger gets the (absolute) measurement uncertainty - *Figure 4*. Looking at the relative measurement uncertainty, which is the absolute measurement uncertainty divided by the load, and usually indicated in percent, the smaller the load is, the larger the relative measurement uncertainty gets. If weighed at the very low end of the balance's measurement range, the relative uncertainty can become so high that the weighing result cannot be trusted anymore. It is good practice to define accuracy (tolerance) requirements for every weighing process. For quantitative analysis, this is even stipulated by USP General Chapter <41>. Weighing in the red area as indicated in the figure will result in inaccurate measurements, as here the measurement uncertainty of the instrument is larger than the required accuracy of the weighing process. Consequently, there is a specific accuracy limit for every weighing instrument – the so-called minimum sample weight, or short, minimum weight, and you have to weigh at least this amount of sample in order to have a sufficiently small uncertainty that satisfies the specific weighing accuracy requirement.

While measurement uncertainty is described in much detail in the respective literature,[7] for weighing small loads on analytical and microbalances – and samples and standards usually are small loads as compared to the capacity of the balance – the dominant contribution factor to weighing un-

*Continued on page 42.*

certainty stems from repeatability (expressed as the standard deviation of a series of weighings). This is also reflected in USP General Chapter <41> as discussed above.

Even though adherence to this USP requirement seems to be straightforward, many companies still have issues with the correct interpretation. While environmental influences and operator variability, which contribute to indeterminate errors and consequently to possible changes or fluctuations of the reading of a weighing device, are discussed later, another misconception which is prevalent in the industry is briefly discussed now. Many companies wrongly believe that the weight of the tare can also be considered in the minimum weight. In other words, they believe that if the tare weighs more than the minimum weight, any sample quantity can be added and USP<41> is automatically fulfilled. This would mean that with a large enough tare container you could even weigh a microgram on a 5-place balance and still comply with the uncertainty requirement of 0.1%. Such an extreme example clearly shows us that this widespread misinterpretation indeed does not make any sense. For this reason, USP has attempted to clarify this issue in the latest draft revision of General Chapter <41>:[8]

*"Amount weighed is not the tare or gross weight. For example, the weight of the sample container or the weighing paper is not included in the amount weighed to determine if repeatability is satisfactory."*

The minimum weight of balances is furthermore not constant, but varies over time. This is due to changing environmental conditions that affect the performance of the instrument, such as, for example, vibrations or draft. The operator himself also adds variability to the minimum weight, as different people might weigh differently or with a different skill level on the balance. In order to ensure that you always weigh above the minimum weight as determined at calibration (at a particular time with particular environmental conditions by a particular qualified person), it is highly recommended to apply a safety factor - *Figure 5*. The safety factor describes that you would only weigh sufficiently above the minimum weight as determined at calibration. For manual weighing, a safety factor of 2 is commonly used, provided there are reasonably stable environmental conditions and trained operators. For very critical applications or a very unstable environment, an even higher safety factor is recommended.

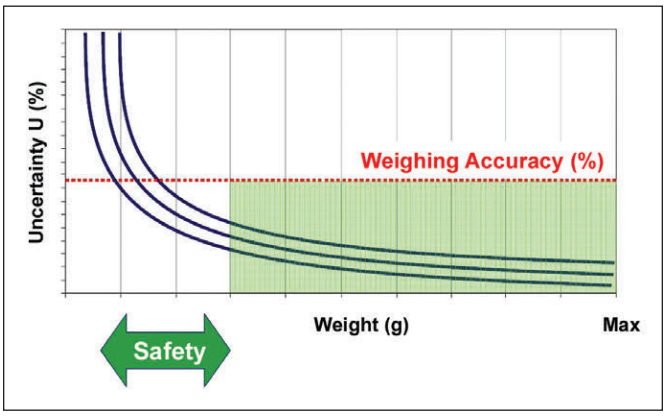


Figure 5. Safety factor: variability of the relative measurement uncertainty due to changing environmental conditions and influences introduced by the operator. Weighing in the green area guarantees adherence to the weighing accuracy requirements (application of a safety factor).

The following discussion will look at the typical USP minimum weight and the recommended safety factor for automated gravimetric dosing systems as compared to manual weighing systems. Provided the same weighing module is used in both instruments, generally the minimum weight for automated dosing systems is significantly lower as compared to the equivalent conventional weighing system. One main reason is that environmental effects – especially drafts and temperature differences between balance and sample - are more efficiently prevented when using automated dosing systems. Furthermore, the variability introduced by the operator is completely removed. The exclusion of the operator variability and the efficient compensation of environmental effects allows for applying a smaller safety factor for automated weighing systems, typically 1.5 instead of 2. Consequently, sample sizes can be chosen much smaller for automated weighing systems, typically smaller by a factor of 3 as compared to manual weighing. While usually 50 mg are weighed manually on a semi-micro balance, an automated dosing system using the same technology typically allows for weighing only 15 mg.

To summarize the discussion on weighing: the most important measure to guarantee accurate weighing – and consequently to avoid the possibility of OOS due to weighing – is the determination of the minimum weight of the balances. Consequently, it is important to always weigh above the minimum weight in order to comply with the respective accuracy requirements. For automated dosing systems, the minimum weight is significantly smaller as compared to manual weighing. It is good practice to apply a safety factor in order to compensate the variability of the minimum weight due to different operators and changing environmental conditions; however, the safety factor can be chosen significantly smaller for automated weighing systems as environmental effects are reduced and the variability introduced by the operator is completely removed.

## Volumetric Addition of Diluent

Some of the key steps in sample preparations involve the use of volumetric glassware. A Google search of the internet for volumetric flask information shows that the production process which created flasks with accuracies similar to what we have today occurred about 75 years or so ago. With this discovery, one realizes that we have basically been using the same system for sample preparations for the past 75 or more years without any improvements. Our instrumentation has dramatically improved, but our sample preparation has been stagnating for nearly a hundred years.

What are some of the errors that are associated with volumetric glassware? A paper published by Coleman and Harris from NIST in 2005[9] states the failure rates of new glassware to meet the Class A specifications have been found to be as

high as 50%. This finding may not be too surprising since there are a lot of vendors for glassware with a number of them having some very cut rate pricing. Maybe you get what you pay for after all. Furthermore, vendors that have poor quality glassware can be a problem when your purchasing department decides to change to a lower cost vendor without consulting the analytical department and without having a proper evaluation of the new vendors performed.

There are other pitfalls associated with volumetric glassware. First, the temperature changes of the solution which result in volume changes can cause errors if the working temperature is significantly away from the volumetric calibration point of 20°C. These temperature excursions may be caused by endothermic and exothermic mixing of solvents. In addition, a sonicator, which is often used to aid dissolution of solids, can cause a significant increase in the temperature of the solutions. Additional information regarding the operating temperature ranges for Class A glassware can be found in a UKAS publication on traceability of volumetric apparatus.[10] Second, ill fitting glass stoppers and hollow stoppers that may be damaged, which allow some leakage of the solvent into stopper, can introduce additional errors.

A significant problem with reusing any item in the laboratory, such as volumetric glassware, is contamination from other products or reagents. It's very difficult, if not impossible, to qualify a glassware washing system in development due to the number and variability of the products tested; therefore, it is very important to always pre-rinse and post rinse the glassware with the appropriate solvents to minimize this. Unfortunately, this leads to solvent waste and is time consuming.

There have been a number of OOS investigations where the analyst has forgotten to pre-rinse his volumetric flasks. But in fact, it just wasn't one analyst forgetting, but two since someone must have forgotten to perform a post rinsing operation too. The problem created by this repeating issue is how do you justify a CAPA that says your retraining is addressing the problem when in fact is doesn't. How do you know which analyst didn't do the post-rinsing, do you retrain all analysts? If people continue to forget, what are the next steps? Do you spend hundreds of thousands of dollars on a system to try and remove the contaminants from the glassware? Some companies have. But does it really make sense to spend that much money on 100-year-old technology?

Coleman and Harris also suggested in their paper that the calibration of the glassware should be verified at least every 10 years. This could be a very expensive process knowing that the number of volumetric flasks in a department can be very large. It would probably be cheaper just to throw them all away.

In Table B, the published NIST relative percent errors associated with each size of volumetric glassware are listed. In each case as the size decreases to the lower values, the errors increase significantly. The errors associated with the Class A glassware that does not meet the specification would be even larger, as mentioned previously concerning the high failure rates.

| Pipettes | | Flasks | |
|---|---|---|---|
| Volume (mL) | Relative % Error | Volume (mL) | Relative % Error |
| 1 | 0.60 | 5 | 0.40 |
| 2 | 0.30 | 10 | 0.20 |
| 3 | 0.33 | 25 | 0.12 |
| 4 | 0.25 | 50 | 0.10 |
| 5 | 0.20 | 100 | 0.08 |
| 10 | 0.20 | 200 | 0.05 |

Table B. Relative percent errors for Class A glassware.

Aside from the significant increase in the relative percent error of the smaller glassware, the smaller glassware is also very technique dependent when it comes to manual manipulations. For example, a study of pipette in one company found that many of the analysts could not properly use a pipette smaller than 2 mL in size. The range of errors found in the sample preparations using smaller pipettes averaged about 2% with some as high as 5%. These errors seemed to be due to not allowing the proper drain time for the smaller pipettes and the condition of the pipette tips.[11]

Another issue that may not be recognized since it has been around for such a long time is the cost of using volumetric glassware. Think about what it takes to keep glassware organized and stored in the laboratory. Everyone who has worked in the lab has probably been charged with ordering and putting away the clean glassware at some point in their career. This is costing some amount of a FTE. The pre and post rinsing on a company wide basis, assuming a very conservative 25 mL use per flask and 10,000 sample preparations, might be costing the company $10,000 or more each year at a $40/liter average solvent cost. This is not a large expenditure, but these costs do add up to a substantial amount and are reoccurring annually especially when you include the waste disposal costs. Additional costs are a lab services group that transports the flasks to and from the washing facility and attrition due to breakage and damage, results in about a 10% loss each year at a cost of about $20 per flask.

Clearly, there are a multitude of good reasons to seek an alternative to using volumetric flasks for diluent addition, which will be explored in more detail later.

## Sample Sonication

Most samples are sonicated to expedite the breakup of tablets, capsules, or powders. Sonication can cause OOS results when there is a lack of robustness in the method. The lack of robustness arises from the improper use of the sonicator and whether or not the instrument is tuned properly. Most sonicators have the following instructions on them:

- Do not place parts or containers directly on the bottom of the cleaning tank. Use a try or wire to suspend items.
- Do not allow the solution to drop more that 3/8 inch below the operating level line with the cleaner on.

However, in our experience, we find few people following those

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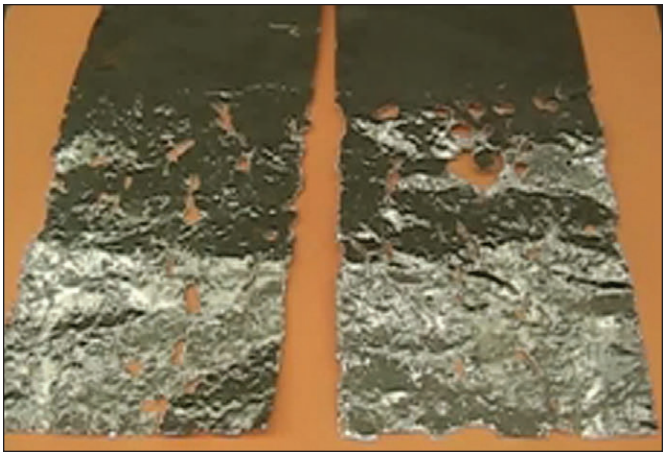

Figure 6. Foils from a tuned and untuned sonicator.

instructions. The pictures in Figure 6 are of a tuned and untuned sonicator. The untuned system basically has most of its energy focused in the middle of the bath, where you can see the large hole in the right foil. Therefore, the energy of the system can vary significantly depending on the placement of the sample into the bath.

## Sample QS'ing and Final Mixing

One would think that the QS'ing and the final mixing step would not be much of an issue, but they can and have been a source of OOS results for two reasons. First, the solution in the flask needs to be returned to room temperature or as close to the 20°C calibration temperature of the flask as practical. Failure to do this introduces an additional source of error into the sample preparation process.

Second, many methods need to have better instructions for the final mixing after the QS'ing step. Most methods only state to mix well without realizing that a volumetric flask is an extremely poor mixing vessel that requires it to be inverted a number of times to ensure proper mixing.

## Sample Labeling

Labeling can cause OOS results due to label mix ups, but the most significant issues here are usually at safety and GxP audit times. Regardless of what a labeling SOP in the company states, when flasks in laboratories are examined, the labeling ranges from the very minimum to the very detailed. Of course, all of these permanent marker labels must be removed before sending them out to be washed and that necessitates the use of methanol or acetone and wiping down the flasks, consuming time and wasting solvents.

## Improving the Sample Preparation Process

Faced with issues and dealing with the technologies currently in use, there are usually only two choices. You can change within the technology or select a new technology. If you want to reduce your relative uncertainty, you could use larger volumetric glassware, but that doesn't meet the needs of efficiency and wanting to have a smaller footprint or go greener. You also could change the technology, for example, replace pipettes with microliter syringes or move from volumetric to gravimetric dispensing.

There are systems on the market that do a very good job of handling liquids using microliter syringe systems and small robotic manipulators that move small vials around. However, the downside to these systems is the additional time and resources it takes to ensure that cross contamination does not occur when the syringes are reused. For example, once a sample has been diluted, the syringe needs to be rinsed properly to ensure that there is no sample carryover to the next operation. Appropriate washing steps can be included, but this needs to be checked and verified during the method development process to ensure that the washing is adequate. In addition, since the solvent used to perform the final syringe cleaning may not be compatible with the next operations, a way needs to be established to transition the system from method to method or even sample to sample. This is especially true if aqueous and non aqueous solvents are being used. Ideally, a system is needed that eliminates this cross contamination issue.

## Gravimetric Sample Preparation

One system which has addressed this problem eliminates the volumetric approach completely. Instead, a gravimetric approach is used to deliver both powders and liquids using individual dosing heads to a target container placed on a balance - *Figure 7*. Since the powder dosing heads are disposable and the solvent dispensing heads are exclusively used for a single solvent, any risk of cross contamination is eliminated. These automated systems are being adopted by analytical laboratories in the pharmaceutical industry. Gravimetric Sample Preparation (GSP) is defined as preparing the sample using gravimetric measurement only. This means weighing


Figure 7. Gravimetric dispensing system.

not only the solid, but also weighing the solvent on an analytical balance to enable a precise concentration of solution to be prepared.

It is universally accepted that a gravimetric measurement is intrinsically more accurate that a volumetric measurement. In fact, pipettes and volumetric measuring equipment are calibrated using gravimetric methods. So why are people still weighing solids and powders on a weighing paper, transferring them into volumetric flasks, and subjectively reading the meniscus to prepare a specific concentration? Gravimetric Sample Preparation means that weighing papers and volumetric flasks are no longer necessary.

We have already discussed how the addition of the diluent by volumetric dosing introduces a manifold of indeterminate handling errors, such as reading the meniscus incorrectly or using the glassware at temperatures where thermal expansion causes the limit of error to be exceeded. Gravimetric liquid dosing avoids these non-quantifiable handling errors, furthermore, weighing liquids at gram levels is very accurate because it results in a completely negligible measurement uncertainty contribution of this process step. The amount of diluent is typically far above the minimum weight of the balance, where the hyperbolic shape of the relative measurement uncertainty curve flattens out to almost zero.

With GSP, the exact amount of substance dispensed (whether dispensed manually by spatula or using an automated dosing head) is recorded and used to precisely calculate the amount of solvent to weigh in to the container. Any under or overshoot in powder weighing doesn't require you to waste time adding a tiny amount more or scooping material off the weighing paper with your spatula. The automated liquid dispensing compensates for this and delivers the correct amount of diluent to achieve the required concentration. The sample can then be sonicated and used without the need to be concerned about temperature and mixing.

With the use of a gravimetric system, there will be a switch over from expressing concentration in mg/mL to mg/g and this may be a difficult change for many laboratories to make due to existing SOPs, but the benefits are large. In the gravimetric method, you would simply convert the mg/mL concentration over to mg/g using the density of the diluents. These densities do not have to be known exactly since methods are designed to have a concentration range of ±5% or more to allow for variability in the weighing operation. Of course, if you begin originally using the gravimetric approach during method development, no density values are required.

In terms of data management, there are also distinct advantages of automated gravimetric sample preparation in comparison with the manual volumetric approach. The manual approach requires hand transcription which has a high error-risk, and it relies on the diligence of each individual analyst. It is simply not possible to digitally record which size of volumetric flask was used automatically.

With an automated approach, the data transcription is automated. All samples and solvents are identified by Radio Frequency Identification (RFID) to eliminate the possibility of weighing the wrong sample. All weighed samples are documented electronically (target weights, actual weights, and concentrations achieved) and the data is fully traceable.

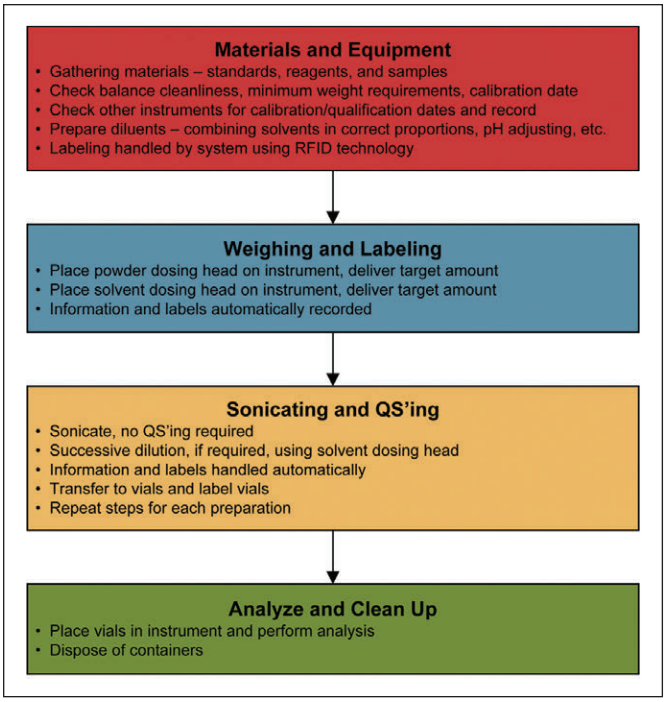


Figure 8. New simplified sample prep workflow using a gravimetric approach.

Labels with pre-defined fields can be printed automatically for immediate application to the vial containing the prepared solution. This addresses the issues with accuracy and consistency of labeling, which were discussed in the context of the manual approach.

Additional benefits of gravimetric sample preparation are that the minimum weight is lower and the analyst is not constrained to make a volume based on the size of volumetric flask available. These two factors combined mean that smaller amounts of sample can be used, smaller volumes of solutions can be prepared, less solvent is consumed, and there is less waste to dispose of. The automated nature of the process also makes it safer for the analyst.

The new gravimetric sample prep workflow is shown in Figure 8. When you compare this to the previous volumetric workflow, Figure 3, you will see a significant reduction in the number of steps. This means that the process is much more efficient and a significant amount of time is saved in the sample preparation workflow. More importantly, the steps that have greatest potential to cause OOS results have been eliminated.

## Reducing Errors

To directly compare the manual volumetric and the automated gravimetric methods, let's look at a simple preparation comparing the two techniques. If the method requires a 0.5 mg/mL concentration then using a volumetric system, one would use a 200 mL volumetric flask and weigh out 50 mg of material. Table A shows the types of errors that may be found in this simple procedure. As you can see from the table, for

*Concludes on page 46.*

gravimetric sample preparation, the number of determinate errors has been reduced and the indeterminate errors which tend to be much larger than the determinate ones are essentially eliminated or accounted for.

## Conclusion

Reducing the occurrence of OOS results in the laboratory requires close attention to the details of where errors can occur, a critical evaluation of the overall process workflow, and a concerted effort to change those practices that lead to OOS results or errors in the data. This error reduction cannot occur using the old technologies, so new technologies must be brought into the laboratory to finally improve the data quality that is being generated by laboratories around the world. In addition, most companies want and need to achieve higher productivity with the same or less resources. This efficiency cannot occur without a fundamental change in the way we perform our sample processing, which has had little improvement for the best part of a century and still accounts for more than 60% of our time spent in the laboratory. Gravimetric sample preparation is an innovative way to eliminate or drastically reduce the variability in the sample processing steps thereby significantly reducing the occurrence of OOS results.

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11. Personnel experience by author C. Ray where he tested analyst in his group.


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**This article presents a risk-based approach to continuous quality verification of cleaning procedures.**

# A Quality Risk Management Approach to Review and Monitor Cleaning Processes

by Ian Campbell and Dominic Thibeault

Cleaning processes should be continuously monitored and evaluated at defined intervals and re-validated as necessary. Further assurance that the process remains in a state of control also can be gained through monitoring routine production, including using Process Analytical Technology (PAT), where applicable.

The application of quality risk management principles can effectively address requirements for cleaning process reassessment and revalidation. A systematic quality risk assessment can serve to identify where additional oversight might be required as well as serving as a guide to the extent of the oversight.

A holistic approach to the review of cleaning programs should be taken to ensure adequate controls continue to be in place after the initial cleaning validation studies have been completed. A high level risk review or Preliminary Hazards Analysis (PHA) of the operational and environmental controls is performed as a preliminary step. This is followed by a detailed quality risk assessment of the cleaning process itself using a Failure Modes and Effects Analysis (FMEA) approach to assess the risk associated with the cleaning process and identify if and where any risk mitigation measures might be needed.

This article presents a risk-based approach to periodic revalidation of cleaning procedures as an approach to maintaining the validated state. The application of quality risk management allows for a systematic, science-based approach to the evaluation of cleaning procedures to ensure a continued state of control.

## Introduction

Good Manufacturing Practices (GMP) dictate that all procedures employed for the cleaning of product contact surfaces in the GMP environment undergo (cleaning) validation studies. The ultimate purpose of cleaning validation is to ensure that the controls in place are adequate to ensure the risk of cross contamination is at an acceptable level and to adequately contain the transference of product from the surrounding environment. Typically, cleaning validation programs for multi-product facilities are based on an equipment/product "matrix" which identifies worst case "marker" molecule or product to challenge cleaning procedures through validation studies.

Studies are typically undertaken wherein a marker molecule is used to challenge the cleaning procedure to ensure that the cleaning procedure is effective in removing residues to an acceptable level. While studies identified through a cleaning validation matrix may serve to ensure that a cleaning process is effective upon implementation, periodic review is required to ensure the consistent performance of the validated cleaning procedures.

There are many controls in place to prevent cross contamination in a pharmaceutical manufacturing facility. These controls range from environmental controls, such as ventilation systems controlling the number of air changes to the application of closed systems to contain production activities. In a multi-product manufacturing environment, cleaning procedures are generally the most direct (or primary) control of product carryover from one batch to the next. Periodic monitoring and revalidation of cleaning procedures can serve to oversee this control and determine if any process drift might be occurring over time.

An evaluation of the potential risk and recommendation for additional controls or

*Continued on page 50.*

risk mitigation strategy is presented in this document. Revalidation of the cleaning procedures on a periodic basis as well as increased monitoring of the environment can serve to substantially mitigate the risk of cross contamination or product carry over.

### *Multiple Product Manufacturing Sites*

In pharmaceutical manufacturing facilities where the manufacturing equipment is used to manufacture multiple products, self-containment, dedicating equipment, or the use of disposable equipment is not always practical. A Risk-Based Approach (RBA) can be applied to determine if existing cleaning validation studies are adequate to ensure the risk of cross contamination is at an acceptable level and that the transference of product to the environment is adequately contained.

The following practices are a necessary foundation for compliance and serve to determine the level of control in the evaluation of cleaning procedures for product contact surfaces:

- Cleaning validation studies are completed and have demonstrated a robust process.
- Cleaning practices related to indirect product contact surfaces are evaluated through an environmental monitoring program.
- A robust training program is in place to ensure that cleaning procedures are consistently applied.
- Changes to cleaning procedures are evaluated through the change control system where the validation impact is determined and any appropriate studies are performed as required.

While the aforementioned evaluation allows us to confirm that adequate procedures and controls are in place, a systematic approach to periodic review including revalidation, if necessary, may be indicated to increase assurance that there are no residual risks above an acceptable threshold limit.

### *Quality Risk Management Application*

As recommended for any risk assessment, a multidisciplinary team made up of the appropriate Subject Matter Experts (SMEs) should perform the risk assessment. This group should include SMEs in validation, quality, engineering, and operations. Each SME should have sufficient expertise to assess the overall risk in their particular functional areas and be capable to critically assess the risks presented by other team members. The responsibility of each team member is to review the risk assessment according to their area of expertise to ensure quality and compliance risks have been identified and accurately evaluated.

A two step approach to evaluation of risk is recommended where a higher level overview of the controls is performed by the team using the Preliminary Hazards Analysis (PHA) approach[1] (informal risk assessment) of the controls in place to support the general cleanliness of the environment, followed by a more formal risk analysis focusing on the primary controls using a Failure Modes and Effect Analysis (FMEA). As cleaning validation serves as the primary oversight of cleaning procedures, it should be part of both the informal and formal risk assessments as seen in Figure 1.

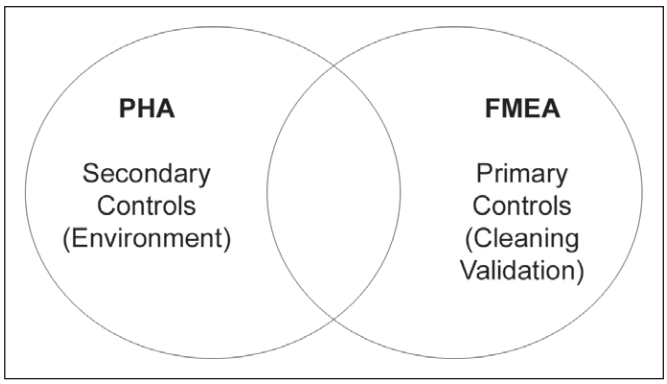


Figure 1. Two step risk assessment.

## PHA

A Preliminary Hazard Analysis (PHA) is first performed to assess the environment where the cleaning processes are applied in order to identify any high level potential for failures. These controls can be considered as indirect or secondary to the cleaning procedure itself. This step is essentially an assessment of the risk of cross contamination or product carryover through the manufacturing environment itself. A qualitative assessment is performed to review the controls in place and identify any potential risk. Provided that no high risk areas have been identified with the secondary controls, the requirements of periodic review, including potential revalidation can be assessed through a FMEA.

The controls in place to ensure a clean environment should be evaluated as part of the PHA, such as an overview of how the premises are laid out, as well as the flow of material taken in the context of the nature of the operations, e.g., dust generating open system vs. closed system. A high level review of the cleaning validation program also should be part of the PHA to ensure the necessary structure is in place and that it is serving the purpose of controlling carry over. A more detailed analysis of the actual cleaning validation studies can then be performed through the FMEA step. In performing a preliminary hazards analysis, the following aspects should be considered:

### *Cleaning Validation Program Review*

A review of the cleaning validation program is performed to ensure that adequate studies have been performed on each cleaning procedure as per current Good Manufacturing Practice (cGMP) expectations. More than one application of a cleaning validation study may exist where it was judged necessary to gather supplemental information (e.g., to sup-

port a proposed change). A cleaning Validation Master Plan (cVMP) also should be in place and reviewed periodically and updated to include any Corrective Action and Preventive Action (CAPA) or change control requirements.

The cVMP should outline the various elements which comprise cleaning validation, i.e., matrices, establishing limits, analytical methodology, sampling procedures, change control, etc. Cleaning validation is used to provide a high degree of assurance that a specific cleaning procedure, when performed appropriately, will consistently clean a particular piece of equipment to a predetermined level of cleanliness. Factors which are considered in setting appropriate limits are batch size, dosing, toxicology, and equipment size or surface area. Any modification to a cleaning procedure, addition of a new product to the site product portfolio, or modification to existing products is documented in the site change control system and analyzed by an SME in cleaning validation. Supplemental studies may be recommended, if necessary.

### *Operation Review*

A review of the controls in place to ensure that the manufacturing activities are performed in areas that are designed to prevent environmental contamination and contamination from another product. All handling of materials and products from receipt and quarantine, sampling, storage, labeling, dispensing, processing, packaging, and distribution should be performed according to clearly defined procedures (and must comply with the principles of Good Manufacturing Practice). Manufacturing and packaging should be followed by appropriate cleaning, which includes a final visual inspection, line, and room clearance. Measures to prevent microbial proliferation should be taken (e.g., sanitization) and their effectiveness should be monitored through an environmental monitoring program.

### *Personnel/Material Flow*

As further part of the review of the environmental controls, the potential for cross-contamination due to the flow of personnel, equipment, and material throughout the general manufacturing area should be evaluated, including any appropriate gowning practices and procedures.

### *Premises*

A review of the room pressurization scheme should be performed to ensure that it is adequately designed to prevent cross-contamination for the activities performed. This may identify an increased burden on the cleaning procedure or affect recommended storage parameters (e.g., protection of cleaned equipment). A review of the building management system or other appropriate indicators used to monitor and control the HVAC system should be undertaken. These controls must include appropriate airflow (such as fresh air and exhaust) to meet required conditions (such as the temperature, relative humidity, and room pressure). All production, dispensing, and sampling rooms should be appropriately balanced to their adjacent environments and adequate filtration should be effected (i.e., HEPA filters).

Part of the review of the premises should include an evaluation of the required environmental conditions (including temperature, humidity, pressure differentials, and HEPA filtration) to ensure they are appropriate both to the products handled and to the operations undertaken within them. This may include appropriate air extraction for all critical operations through the use of dust collectors and house vacuum, where appropriate. The architectural finishes in these areas also should be designed to facilitate cleaning (and comply with GMPs).

## FMEA (Risk Analysis of the Primary Controls)

In order to analyze primary controls and determine the requirements to periodically review the cleaning procedures and to establish the appropriate priorities, a formal risk assessment should be undertaken. The FMEA model can be applied where the risk of failure can be evaluated as to its likelihood of occurrence, severity, and the detectability. The risk question to be considered is "what is the risk that this cleaning procedure could fail and allow carryover of product, cleaning agent, or microbial residue."

The standard FMEA approach can be expanded upon in order to allow for equally weighted questions to be asked for each category. The following factors are considered in the risk analysis:

**Likelihood of Occurrence**
- number of different products[2] cleaned by the procedure
- number of applications of cleaning per predefined period (e.g., annually)
- degree of difficulty to clean

**Severity**
- toxicity of ingredients cleaned
- dosing profile of ingredients cleaned

**Detectability**
- number of cleaning validation executions
- date since last cleaning validation execution

Each category is explained in more detail as follows:

### *Likelihood of Occurrence*

#### *Number of Products Cleaned*

The number of products cleaned provides a high level indication of the potential of cross contamination due to the inherent probability that a changeover cleaning will occur after cleaning. Multiple product equipment which is subject to continuous changeover from one product type to another presents a higher degree of risk of carryover than equipment that is dedicated to a single product. The relative risk rank can be determined by distributing the total product load across a scale of 1 to 10. Table A demonstrates a potential risk ranking for a multi product manufacturing plant with more than 100 products.

*Continued on page 52.*

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Products Cleaned** | 1 or less (no actives) | ~15 | ~30 | ~40 | ~50 | ~60 | ~70 | ~80 | ~90 | 100 or more |

Table A. Risk ranking for a multi-product manufacturing plant with more than100 products.

| **Risk Rank** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Applications of Cleaning Procedure per Year** | 1 / year | 1 / Q | < 1 / M, > 1 / Q | 1 / M | 2 / M | 3 / M | 1 / W | 2 / W | > 2 / W, < 1 / D | 1 / D |

Table B. Number of applications of the cleaning procedure scale.

### *Number of Applications of Cleaning Procedure per Year*

The number of applications of the cleaning procedure per given period (e.g., year) provides an indication of the potential of cross contamination based on frequency. Equipment which is frequently cleaned and changes from one product type to another presents a higher degree of risk or carryover than an equipment that might undergo lengthy campaigns and is continuously processing the same product. The relative risk rank can be determined by factoring in the number of applications of the cleaning procedure across a scale of 1 to 10 as demonstrated in Table B.

### *Cleaning Difficulty/Dismantlability*

With the exception of Clean in Place (CIP) and Clean out of Place (COP) systems, cleaning procedures are predominately operator dependant. The degree of difficulty can thus be based on general equipment design and the amount of manipulation required to clean a given piece of equipment. The cleaning procedures are evaluated to determine the ease at which the equipment could be dismantled for cleaning, thus reducing the possibility of buildup of residue in difficult to access locations as well as providing an indication as how much effort was necessary to access areas where residue could potentially be located. It is critical to solicit operator feedback to determine the overall level assigned for this assessment. The results can then be distributed across a scale of one to 10 where one is assigned to the easily cleaned equipment and a 10 is assigned to equipment that is judged more difficult to clean as demonstrated in Table C.

## ***Severity***

### *Toxicity of Ingredients Cleaned*

The toxicity of the ingredients processed (and subsequently cleaned) is evaluated to provide an overall risk of the severity of cross contamination. A residue of a more toxic product being carried over into a batch subsequently processed on the same equipment is considered to be more severe than the residue of a relatively innocuous compound. The levels are determined by reviewing the available $LD_{50}$ or No Observable Adverse Effect Level (NOAEL) data (worst case). $LD_{50}$ data is a good indicator for the risk assessment as the data is readily available and provides a good comparison across a broad range of products. The entire range of toxicity can be divided from across the entire applicable range and distributed across a scale of 1 to 10 as demonstrated in Table D where a range was established as < 1 mg/kg (most toxic) through to > 100,000 mg/Kg (least toxic).

### *Dosing Profile of Ingredients Cleaned*

The potency and frequency of administration of the ingredients processed (and subsequently cleaned) is evaluated to provide an overall risk of the severity of carryover of residue. A residue of a more potent product with a low frequency of administration being carried over into a batch of another product subsequently processed on the same equipment is considered to be more severe than the residue of a less potent, frequently administered compound. The levels are determined through available dosing information where the lowest daily dosage can then be combined with the (maximum) frequency of administration to establish a maximum daily dosage of a

| **Risk Rank** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Degree Dismantled/Ease of Cleaning** | Completely dismantled easily cleaned | very high | high | medium high | medium | low medium | medium low | low | very low | Special precautions required to clean |

Table C. Degree dismantled/ease of cleaning scale.

| **Risk Rank** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Toxicity of Ingredients Cleaned** | $LD_{50}$ > 100,000 mg/kg | $LD_{50}$ > 10,000 mg/kg – $LD_{50}$ < 100,000 mg/kg | $LD_{50}$ 10,000 mg/kg | $LD_{50}$ > 1,000 mg/kg – $LD_{50}$ < 10,000 mg/kg | $LD_{50}$ 1,000 mg/kg | $LD_{50}$ > 100 mg/kg – $LD_{50}$ < 1,000 mg/kg | $LD_{50}$ 100 mg/kg | $LD_{50}$ > 10 mg/kg – $LD_{50}$ < 100 mg/kg | $LD_{50}$ > 1 mg/kg – $LD_{50}$ < 10 mg/kg | $LD_{50}$ < 1 mg/kg |

Table D. Range of toxicity.

| Risk Rank | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Dosing Profile of Ingredients Cleaned (Maximum Daily Dosage) | > 10 mg/kg | > 10 mg/kg < 5 mg/kg | > 5 mg/kg < 1 mg/kg | > 1 mg/kg < 0.5 mg/kg | > 0.5 mg/kg < 0.1 mg/kg | > 0.1 mg/kg < 0.05 mg/kg | > 0.05 mg/kg < 0.01 mg/kg | > 0.01 mg/kg < 0.005 mg/kg | > 0.005 mg/kg < 0.001 mg/kg | < 0.001 mg.kg |

Table E. Dosing profile as indicated by the maximum daily dose.

| Risk Rank | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of CV Executions | More than 24 | 24 | 21 | 18 | 15 | 12 | 9 | 6 | 3 | 0 |

Table F. Number of cleaning validation executions.

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Date Since Last Execution | Less than 1 year | 2 years | 3 years | 4 years | 5 years | 6 years | 7 years | 8 years | 9 years | 10 years |

Table G. Number of years since the last cleaning validation study.

given active ingredient. The dosing profile as indicated by the maximum daily dose can then be distributed across the entire applicable range across a scale of 1 to 10 as demonstrated in Table E where a range was established as < 0.001 mg/kg (most potent) through to > 10 mg/kg (least potent).

### *Detectability*

#### *Number of Cleaning Validation Executions*

The number of (successful) executions of cleaning validation trials can be evaluated to provide an overall indication as to the degree of detectability of a failure. The number of visual inspections undertaken through cleaning validation studies, complimented by surface swabs or rinse samples tested in the analytical laboratory to quantify the amount of residue on the equipment surface after the application of the cleaning procedure, can be used to provide an indication as to the degree of overall level of detectability of failure. The lowest detectability (10) level is assigned to those cleaning procedures that might have been lacking a directly supporting cleaning validation study (e.g., equipment subclass). The highest level of detectability (1) is assigned to the procedures which had undergone the most cleaning validation executions as demonstrated in Table F.

#### *Date Since Last Execution*

The date since the last execution of a cleaning validation study is evaluated to indicate how recently any direct measurement had been made to determine the effectiveness of the cleaning procedure through a validation study. A measure of the lag time since the last cleaning validation swabs were analyzed can be used to provide an indication as to the degree of overall level of detectability that the cleaning procedure is in control, through direct measurement. The lowest detectability (10) level is assigned to those cleaning procedures where cleaning validation studies had occurred earlier on over the course of the cleaning validation program. The highest level of detectability (1) is assigned to the procedures which had been evaluated through more recent cleaning validation studies. The levels from 1 to 10 can be distributed across the range based on the number of years since the last cleaning validation study had been undertaken as demonstrated in Table G.

The outcome of the risk assessment can be used to determine the priorities and frequency of revalidation studies. This approach should be iterative on possibly an annual or bi-annual basis.

*Concludes on page 54.*

## Risk Acceptance (threshold)

The risk priority number can then be determined from the FMEA risk assessment described previously by multiplying the seven factors together. This will provide a range of $1^7$ (lowest risk priority) to $10^7$(highest risk priority) as all factors at the lowest risk through to all factors at the highest risk. The risk priority number is used to provide an indication as to the overall level of risk relative to the degree of oversight of the cleaning procedures in addition to the routine checks in place for each application of a cleaning procedure. A risk threshold can then be assigned in order provide guidance and establish priorities for a risk mitigation strategy.

A risk mitigation strategy is developed to outline the activities and timing required to bring the risk to below the acceptable threshold. The primary objective is to determine when cleaning re-validation studies may be necessary. The cleaning validation studies should be planned to address all procedures where the risk threshold has been surpassed.

A guideline for establishing the risk threshold is to use the midpoint for each category of risk identified through the FMEA process. A risk threshold of midpoint ($5^7$ or 78125) "full scale" is recommended to determine where risk mitigation strategies are required.

Any item where the risk threshold is exceeded should be assigned a mitigation strategy, ideally in the form of a cleaning re-validation study. The risk priority level can be recalculated after the mitigation activity has been completed to determine if the risk has been reduced below the acceptable threshold. If this is not the case, further mitigation strategies should be evaluated.

## Conclusion

A quality risk management approach to the evaluation of cleaning processes may indicate that revalidation is recommended to contain the risk of failure of cleaning procedures below an acceptable threshold. The primary risk reduction and controls strategy described in this approach is revalidation of cleaning procedures and should take the following form:

- Cleaning re-validation of cleaning procedures that have been shown to exceed the acceptable risk threshold through the FMEA analysis outlined in this document.
- Continue to monitor the environment and controls in place including environmental monitoring.
- Reevaluate the risk on an ongoing basis.

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**Pfizer's Vice President of Global Quality Operations discusses the elements and challenges of quality risk management. She provides insight into how Pfizer applies risk management to product quality decisions.**

## PHARMACEUTICAL ENGINEERING Interviews

# Mary Oates, Vice President of Global Quality Operations, Pfizer

by Cathy Middelberg and Jeff Hargroves,
ISPE *Pharmaceutical Engineering* Committee (PEC)

**Mary Oates** received a PhD in analytical chemistry from the University of North Carolina at Chapel Hill and holds an undergraduate degree in biochemistry from Queens College. She began her career at Glaxo in North Carolina as an analytical chemist supporting R&D activities. In 1994, she joined Pfizer as a methods validation scientist. She subsequently held positions of increasing responsibility, including oversight for all post-approval regulatory changes and responsibility for Quality at all manufacturing facilities in North America. Oates is currently Vice President of Global Quality Operations at Pfizer. In this role, she is responsible for Quality oversight of all products made by and for Pfizer for both clinical and commercial use. Oates is actively involved in industry initiatives that are aimed at enhancing product quality. For example, she is the immediate past Chair of the Steering Committee of the Product Quality Research Institute.

**Q** What is quality risk management, and what are the key elements to it?

**A** Quality Risk Management, (QRM), is well described in ICH Q9 as, "a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle." A Quality Risk Management approach to pharmaceutical manufacturing recognizes that protecting the quality of a drug product protects patient safety, and that to protect product quality one must first understand the full range and complexity of both specific and systemic risks, and apply this insight to mitigating those risks. The understanding of risk must be data-driven and based on scientific analysis of data that has been systematically captured (via channels such as, for example, process performance, customer complaints, deviation investigations, internal and external audits and inspections). The active engagement of management focuses the organization on understanding and evaluating risks and underscores the importance of ensuring that actions are taken to mitigate them to acceptable levels. Pfizer's QRM approach, for example, is driven by a top-down commitment to product quality, patient safety and continuous improvement.

**Q** How is risk management different than current/other quality programs?

**A** I think of risk management not as a program, but as a systematic way of thinking about data that is enhanced by project risk management tools such as FMEA (Failure Mode and Effects Analysis), which is ingrained in the way we make decisions at all levels of the organization every day. Appropriate risk management is a critical aspect of a culture of Quality, where all employees understand the positive impact they can have on patient safety, and actively embrace opportunities to do so.

**Q** What is a "quality decision?"

**A** A quality decision, in the pharmaceutical manufacturing environment, is one in which the quality of the product itself is assessed. Quality decisions might determine, for example, the acceptability of a lot for release, the potential impact of quality trends on one or more product lots, or the need for action based on a quality finding. The effective application of risk management focuses the decision-making process on patient safety to enable sound quality decisions.

**Q** What are the current benefits to a risk management program and what do you envision are the benefits in the future?

**A** The primary benefit now and moving forward is that patient safety is protected by the systematic use of a rigorous process rooted in scientific data and knowledge. In addition, the application of a comprehensive, top-down Quality Risk Management approach streamlines the decision-making process by giving all employees at all levels the necessary training and tools to incorporate the thought process into their daily work. Finally, Quality Risk Management is a critical component of a Quality culture.

**Q** What are the typical roadblocks you have seen to the establishment of an effective risk management program?

**A** There can be both internal and external roadblocks. A strong and centralized management commitment to product quality and patient safety is absolutely essential to supporting and encouraging the widespread adaptation and appropriate use of QRM principals and tools. This leadership commitment fosters an effective and agile Quality System that is focused on continuous improvement, detects trends as well as specific issues, and enables a robust notification management process that ensures key stakeholders are aware of critical information and can take all necessary actions. Pfizer, for example, has an outstanding notification to management system that permits visibility to all issues, both product-specific and trends, that may impact marketed products anywhere in the world. This system supports a consistent decision-making process, based on QRM principals and focused on protecting patient safety at all times.

Another potential concern for some organizations may be the inappropriate application of the QRM concept. Management can overcome this by taking the lead, demonstrating the appropriate use of QRM, and ensuring that the focus on patient safety is maintained.

*Continued on page 58.*

***"...QRM cannot be effective in a vacuum – many elements must exist to support it, including management and employee buy-in, standards, training, sharing across the network and a culture that drives continuous improvement and maintains a keen focus on patient safety."***

**Q** What needs to change in the pharmaceutical quality systems to effectively implement risk management?

**A** Implementing QRM into an effective pharmaceutical quality system shouldn't require any changes. In fact, QRM has long been used as a way of evaluating and mitigating risks – only recently has it become formalized through the use of relevant tools and incorporated into existing procedures.

**Q** What does risk management look like at Pfizer, and how does it affect mindsets, behaviors, and the corporate culture?

**A** Pfizer's QRM approach is driven by a top-down commitment to product quality, patient safety and continuous improvement. QRM principals are applied in alignment with Pfizer's robust, organization-wide culture of Continuous Improvement and commitment to Quality Standards. This not only enables a consistent and patient safety-focused process for making quality decisions, but also advances a systematic way of capturing, analyzing and applying data across all levels of the organization.

**Q** How has Pfizer's risk management program been rolled out to the corporation and how is communication maintained?

**A** The first step was to facilitate understanding by defining a common language for a more formal approach to risk management. QRM approaches are governed by Pfizer Quality Standards, which allow sites flexibility in the applications of QRM and its tools. It was also important, early on, to demonstrate how QRM's patient-safety focus aligned with Pfizer's robust quality culture. Examples and best practices were shared across the network, and training – including "risk calibration" workshops – was provided on the use of the specific tools. At the site level, "QRM champions" promote the appropriate and effective use of the QRM thought process and tools.

Pfizer's verification approach to manufacturing system (e.g. equipment, facilities, utilities, and automation) qualification is an example of embedding QRM across manufacturing processes. In 2007, use of Lean/Six Sigma methodology identified an opportunity to simplify and streamline Pfizer's Commissioning and Qualification program, prompting development of a science- and risk-based Verification program. Emphasizing QRM across the product lifecycle, this science- and risk-based approach is designed to ensure the appropriate specification, design and verification of manufacturing systems.

The level of verification rigor and extent of documentation for activities identified within the scope of a project are commensurate with the level of risk to product quality and patient safety. For example, manufacturing system requirements directly relating to product quality and patient safety should be based upon product/process knowledge and understanding (e.g., identification of Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs)), and cGMP requirements. Quality risk assessments should be the basis for the identification of CQA/CPPs for each process that will utilize a given system. This information will be used as a primary input into the Requirement Document and verification strategy for a given system.

The first step in rolling out the Verification program was providing training on the tools and thought process of QRM in general, and identifying specific risk management activities embedded throughout the process. Routine Verification Community of Practice forums were subsequently implemented to discuss case studies from site capital projects, verification performance metrics, continuous improvement initiatives and industry benchmarking. A shared document repository contains project documents and SOPs to enable rapid adoption of best practices and procedures across the users.

This example demonstrates that QRM cannot be effective in a vacuum – many elements must exist to support it, including management and employee buy-in, standards, training, sharing across the network and a culture that drives continuous improvement and maintains a keen focus on patient safety.

**Q** How does risk management affect the manufacturing floor personnel?

**A** It provides a common risk language and evaluation and decision-making tools that employees can apply to identify and protect against risks to product quality and patient safety. The QRM focus on patient safety reinforces and extends Pfizer's established Quality culture across all levels of the organization.

**Q** What capabilities should a firm have in place in order to implement a risk management program?

**A** Pharmaceutical organizations seeking to implement an effective risk management program should have a Quality foundation in place to support its QRM efforts and activities, a leadership commitment to protecting product

quality and patient safety, and an active demonstration of management-level support.

**Q** What do you consider the best resources to help someone design an effective risk management program?

**A** Externally, QRM is becoming more accepted by regulators and industry on a global scale. For example, quality risk management is a requirement of Chapter 1 of the EU GMP Guide Part 1 and an assessment of QRM is an element of inspections. ICH Q9 is an outstanding document and essential guide for those seeking to formally incorporating QRM into their processes.

**Q** How can a risk management program be applied across other functions, such as commissioning and qualification, process validation, engineering or research?

**A** In the pharmaceutical manufacturing environment, risk management is not solely "owned" by the Quality organization. Rather, the risk management concept it is a rigorous thought process that is based on scientific data analysis and can be applied in any setting to understand the impact of potential actions or decisions on product quality and patient safety. The example I shared earlier, of the QRM approach Pfizer uses in verification of its manufacturing systems, highlights how risk management thinking and its tools can be applied to any activity throughout the product lifecycle.

**Q** How can ISPE help facilitate the development of risk management programs?

**A** ISPE can provide forums that, by sharing best practices and examples across the industry and its regulators, can enable a more universal understanding of QRM. This is of benefit to all stakeholders in the pharmaceutical industry, and most importantly, to patients.

# ISPE Announces 2011 Award Winners at Global Annual Meeting

ISPE announced its 2011 award winners at the Society's Annual Meeting held in Grapevine, Texas, USA 6-9 November, recognizing the awardees' contributions to ISPE and the pharmaceutical industry. The 2011 Award winners are:

**Michael A. Arnold, RPh,** received the Max Seales Yonker Member of the Year Award, honoring the ISPE Member who made the most significant contribution to the Society during the past year. Arnold was awarded this honor for his work leading the ISPE Community of Practice (COP) Council through major planning and restructuring efforts, as well as for his involvement in re-designing ISPE's education and conference portfolio for 2012.

**Shinichi Osada and Jane Brown** both received the Richard B. Purdy Distinguished Achievement Award, honoring ISPE Members who have made significant, long-term contributions to the Society.

- **Shinichi Osada** received the Purdy award in recognition of the high impact of his active involvement with the Society both internationally and in Japan. Since 1994, Osada has served on ISPE's International Board of Directors. He was catalytic in introducing the Society's COP concept to Japan, helping to strengthen the local organization and creating a model for other Affiliates in forming local COPs. Osada also served on ISPE's Professional Certification Committee during its formative years, and he provided leadership on the Facility of the Year Awards Committee as well.

- **Jane Brown** received the Purdy award for her consistent, dedicated and passionate service to ISPE over a period of 18 years. Brown has served in numerous leadership roles, culminating in chairing the Board for ISPE's Carolina South Atlantic Chapter, and ultimately serving as Chair of ISPE's International Board of Directors. Since joining ISPE in 1993, Brown has been deeply involved in membership development, regulatory affairs, student and young professional development, the creation of new guidance documents, university relations, and the North American/South American Affiliate Council. She has personally mentored countless professionals, and she is currently leading ISPE's volunteer development efforts.

**The GAMP® Community of Practice** was named the Committee of the Year to honor them for creating a series of GAMP Good Practice Guides. Most recently, this group successfully pioneered ISPE's new conference structure for 2012 with their event, "Improve Productivity with Risk-Based Validation," held in the US and Europe in September and November of 2011.

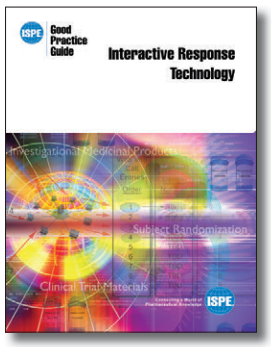
**Pfizer** was named Company of the Year. The organization was recognized for outstanding support as reflected by the large number of Pfizer employees who are Members and volunteers for ISPE. Pfizer-based ISPE Volunteers have engaged in significant active participation in the work of the Society through its many committees, councils, task teams, Communities of Practice, programs, and activities.

**Kristin S. Murray and Stephen P. Reich** received the Roger F. Sherwood Article of the Year Award for their article titled, "Quality Risk Management (QRM) Tool Selection: Getting to Right First Time," published in the July/August 2011 issue of *Pharmaceutical Engineering* magazine.

**The Japan Affiliate** is ISPE's Affiliate of the Year. The Affiliate was recognized for significant success in the areas of membership development and retention. Affiliate Volunteers also produced a Guidance Document for worldwide distribution

*Concludes on page 64.*

# Ground-Breaking Guide Paves Way for Industry Standard on Interactive Response Technology




Interactive Response Technology (IRT) has been used in the pharmaceutical industry for more than 15 years and is becoming a more widespread application to support various clinical trial activities. Yet, there is currently no industry standard on implementing IRT.

In an effort to address the need for guidance on how to use, design and validate, and monitor the use and effectiveness of this technology, ISPE published its first-ever Good Practice Guide on Interactive Response Technology. The Guide establishes minimal functional standards for these systems.

"We wrote this Guide to address regulatory concerns about the way the technology is used, in an effort to show the benefits that wide-spread adaption of IRT could have for the industry, and ultimately, for patients," said Mike Arnold, Guide Chair.

Written by industry experts and influenced by input from the European Medicines Agency (EMA), this Guide provides guidance on how to: successfully implement an interactive response technology to manage key clinical trial activities, particularly expiry date management and program pooling; ensure robustness of the technology, contributing to its effectiveness and reliability; and communicate and foster a standardized, industry-wide approach to critical functionality of Interactive Response Technology when used in managing investigational medicinal product.

*Concludes on page 61.*

# New Guide Addresses Unique Aspects of Project Management in Highly Regulated Pharmaceutical Industry


The practice of Project Management within the highly regulated world of the pharmaceutical industry provides unique challenges and opportunities. The *ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry* addresses those challenges and opportunities. It promotes the integration of GxP with relevant project management activities to ensure that compliance risk is managed both effectively and proactively.

The Guide aims to provide a reference source of good practices for project management for a wide variety of project types within the pharmaceutical industry, focusing on facility and engineering projects, including facility, improvement, and IT projects. The Guide aims to support the development of a common language across the pharmaceutical Project Management community and a way to use generic and specific tools in the context of a pharmaceutical project.

The Guide is intended to be of benefit to Project Managers and other professionals working within the pharmaceutical industry, with the key benefit being an increased potential for successful completion of a pharmaceutical project. Additional benefits include: the collation of a comprehensive list of current good practices to aid project delivery success; the development of a broader knowledge of pharmaceutical projects and project management for a wide variety of stakeholders; and knowledge to mitigate or eliminate risks common to pharmaceutical projects.

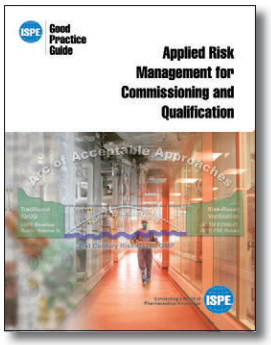
The Guide covers the tools and techniques supporting project delivery, the life cycle of a typical project in the pharmaceutical industry, and how compliance to pharmaceutical industry regulation should be integrated with the project life cycle. The Guide considers new or novel aspects of project management which, although not unique to the pharmaceutical industry, are fundamental to pharmaceutical project success.

## ...Interactive Response Technology

*Continued from page 60.*

Key topics include system design and controls, pooling of supplies, warehousing and distribution, training of investigators and site personnel, and monitoring and managing risk.

# New Guide Bridges Gap between Baseline® Guide and Full ICH Q8, Q9, Q10 Adaptation




The *ISPE Good Practice Guide: Applied Risk Management in Commissioning and Qualification* provides a bridge between the baseline strategies outlined in the *ISPE Baseline® Guide, Volume 5: Commissioning and Qualification* and the more advanced strategies prescribed in the *ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment.*

"With the rapid changes currently underway in the pharmaceutical industry, it's becoming more and more common to find companies at all points of the continuum when it comes to commissioning and qualification best practices," said Steve Wisniewski, one of the Guide authors. "ISPE recognized the necessity of having available guidance to answer questions across the entire spectrum from Baseline to full ICH Q8, Q9, and Q10 adaptation."

"While the *ISPE Baseline Guide, Volume 5: Commissioning and Qualification* remains relevant and is still a viable option, the *ISPE Good Practice Guide: Applied Risk Management in Commissioning and Qualification* serves as an excellent resource for companies that would like to incorporate some elements of Q8, Q9, and Q10, but do not wish to move to full implementation at this time."

***"ISPE recognized the necessity of having available guidance to answer questions across the entire spectrum from Baseline to full ICH Q8, Q9, and Q10 adaptation."***

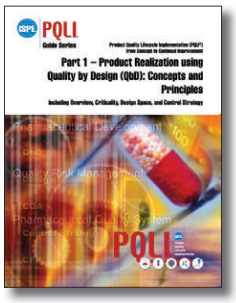
The *ISPE Good Practice Guide: Applied Risk Management in Commissioning and Qualification* describes how organizations can move from established baseline practice to a more efficient science- and risk-based framework. It illustrates the application of Quality Risk Management to traditional commissioning and qualification practices, linking traditional terminology and approaches to the newer science- and risk-based specification and verification terminology and approaches applied in ICH Q8, Q9, and Q10, ASTM E2500, and *ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems and Equipment.*

The approach described in the *ISPE Good Practice Guide: Applied Risk Management in Commissioning and Qualification* allows companies to achieve the benefits of a science- and risk-based model by outlining bridging strategies for organizations with well-established qualification-based Quality Management Systems and providing a roadmap showing the spectrum of potential approaches for this transition.

# New Good Practice Guides Focus on Quality by Design Principles and Practices

ISPE has released Parts 1 and 2 of a new series of Good Practice Guides on Product Quality Lifecycle Implementation (PQLI®). These two new Guides comprise the official first and second volumes of a planned series of PQLI Guides, which collectively address product and process development through a Quality by Design (QbD) approach that covers the entire product lifecycle. The series uses ICH guidelines Q8 (R2) Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System as a basis, together with other relevant ICH guidelines.

"In recent years, both the industry and regulator have realized the importance of designing product quality into the process itself," said PQLI Project Manager John Berridge. "Quality cannot be added during the testing phase; it must be built-in by design. The PQLI Guide Series gives industry personnel a roadmap for how to build quality into their processes, from product conception to continual improvement after the product is brought to market."

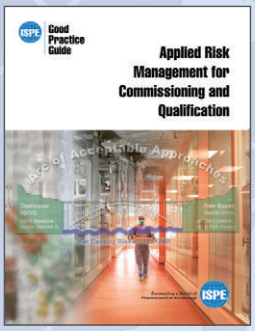



The first Guide in the series, *Part 1 – Product Realization using QbD, Concepts, and Principles,* is focused on the topics of criticality, design space, and control strategy. Part 1 addresses product and process development, transfer to, and establishment of, commercial manufacture using science- and risk-based approaches. It also includes an introduction to, and overview of, the Guide sections.


The second Guide, *Part 2 – Product Realizations using QbD, Illustrative Example,* presents a small molecule case study developed by the ISPE PQLI teams. The case study provides details of the application of the approaches to product and process understanding using quality risk management. Part 2 also examines many case studies in the public domain using ICH guidelines Q8 (R2), Q9, Q10, and other relevant ICH guidelines.

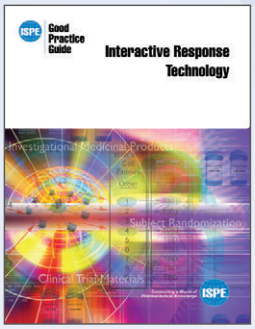
# New Releases!

## ISPE Good Practice Guides




**Applied Risk Management for Commissioning and Qualification**


**Project Management for the Pharmaceutical Industry**




**Interactive Response Technology**

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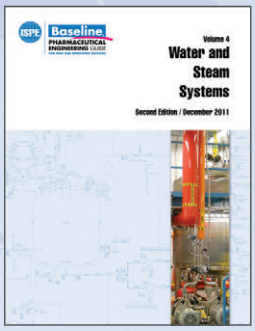
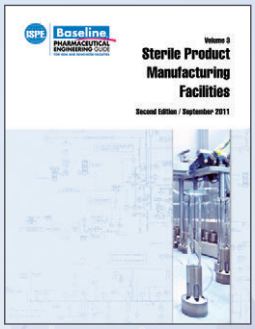
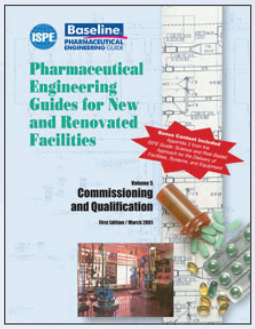
## ISPE Baseline® Guides




**Water and Steam Systems (Second Edition)**

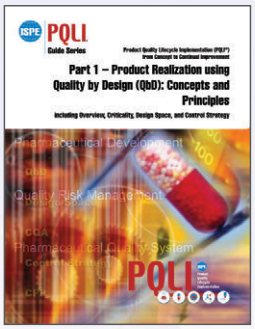



**Sterile Product Manufacturing Facilities (Second Edition)**

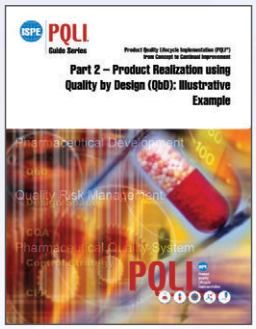



**Commissioning and Qualification with NEW value–added content**

## Product Quality Lifecycle Implementation (PQLI®) from Concept to Continual Improvement




**Part 1: Product Realization using QbD, Concepts and Principles**




**Part 2: Product Realization using QbD, Illustrative Example**

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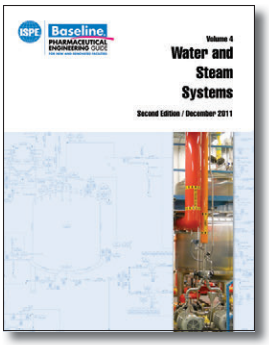
# Updated Water and Steam Guide Addresses Decade of Changes in Regulations and Industry Practices

ISPE has released the long-awaited *ISPE Baseline® Guide Volume 4: Water and Steam Systems (Second Edition)*. The revised and expanded second edition builds on the groundbreaking Water and Steam Systems Guide first published ten years ago. The second edition has been completely revised to address changes in industry practices and global regulations over the past decade. Additionally, this comprehensive, industry-driven document will promote consistent and practical interpretation of regulatory requirements for water and steam systems worldwide. It includes tools to help pharmaceutical manufacturers meet safety requirements while avoiding unnecessary cost.

The Second Edition in individual download format will be available 15 December. The bound version will be available 6 January 2012.

This Guide, which is the only comprehensive guidance of its kind, aims to assist with the design, construction, operation, and maintenance of new water and steam systems that meet current Good Manufacturing Practices (cGMPs) and comply with existing regulations and related guidance. The Guide was written by a global team of critical utilities experts with a combined experience of more than 500 years. Much of the team responsible for the original Water and Steam Systems Baseline Guide has returned to contribute to the revised Guide, providing continuity and longevity of vision to the Guide's contents. The Guide also has been reviewed by the US Food and Drug Administration (FDA), and their comments have been taken into consideration in the final version of the Guide.




The *ISPE Baseline® Guide: Water and Steam Systems (Second Edition)* has been expanded to include new chapters on laboratory water systems and the latest theories and industry practices addressing the rouge phenomenon in high purity water and pure steam systems. New chapters also cover microbiological considerations, such as biofilm formation, use of sanitizers, sampling, testing, and control levels, as well as the overall impact of microbial considerations on unit operations and finished water. PE

# ISPE Announces 2011 Award Winners at Global Annual Meeting

*Continued from page 60.*

that has been one of ISPE's most downloaded documents ever. These accomplishments are especially noteworthy in light of unexpected challenges the Affiliate faced due to natural disasters that took place in the region this year.

## North American/South American Affiliate Council Awards

**The Boston Area Chapter** was awarded the North American/South American Affiliate Council Platinum Grand Award for Excellence and Innovation. This is the third year in a row that the Boston Area Chapter has received this honor. Runners-up for this prestigious award included:

- **The San Francisco/Bay Area Chapter** won the North American/South American Affiliate Council Platinum First Place Award for Excellence and Innovation for medium-sized Chapters. This is the second year in a row that the San Francisco/Bay Area Chapter has won this award.
- **The San Diego Chapter** won the North American/South American Affiliate Council Platinum First Place Award for Excellence and Innovation for small Chapters. The San Diego Chapter also received this honor in 2010, making this the second straight win for the Chapter.
- **The Carolina-South Atlantic Chapter** won the North American/South American Affiliate Council Grand Award for Innovation in Membership Services.
- **San Francisco/Bay Area Chapter** won the North American/South American Affiliate Council First Place Award for Innovation in Membership Services.
- **The Boston Area Chapter** won the North American/South American Affiliate Council Grand Award for Innovation in Programs and Events.
- **The New Jersey Chapter** won the North American/South American Affiliate Council First Place Award for Innovation in Programs and Events for the second year in a row and the North American/South American Affiliate Council Grand Award for Innovation in Student Programs.
- **The San Diego Chapter** won the North American/South American Affiliate Council First Place Award for Innovation in Student Programs.

**The University of California San Diego Student Chapter** is the 2011 Student Chapter of the Year Award Winner. They are sponsored by the San Diego Chapter.

**The International Student Poster Competition Award** in the Graduate Category went to **Diane Darlington** of North Carolina Central University, Carolina-South Atlantic Chapter, and the winner in the Undergraduate Category was **Ryan Lojek** of Villanova University, Delaware Valley Chapter. PE

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## Water Treatment and Purification

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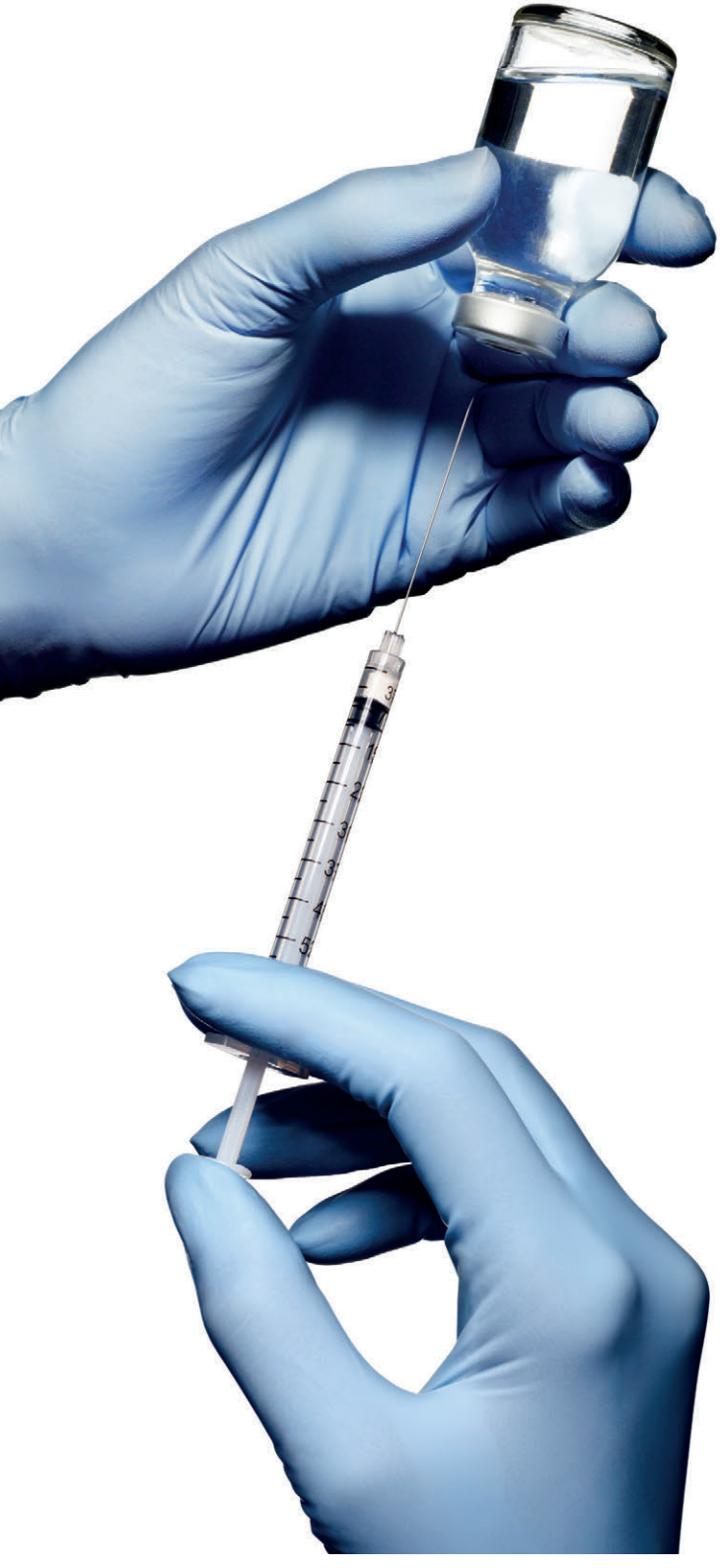
# Advertiser's Index

# A healthy injection for your business



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