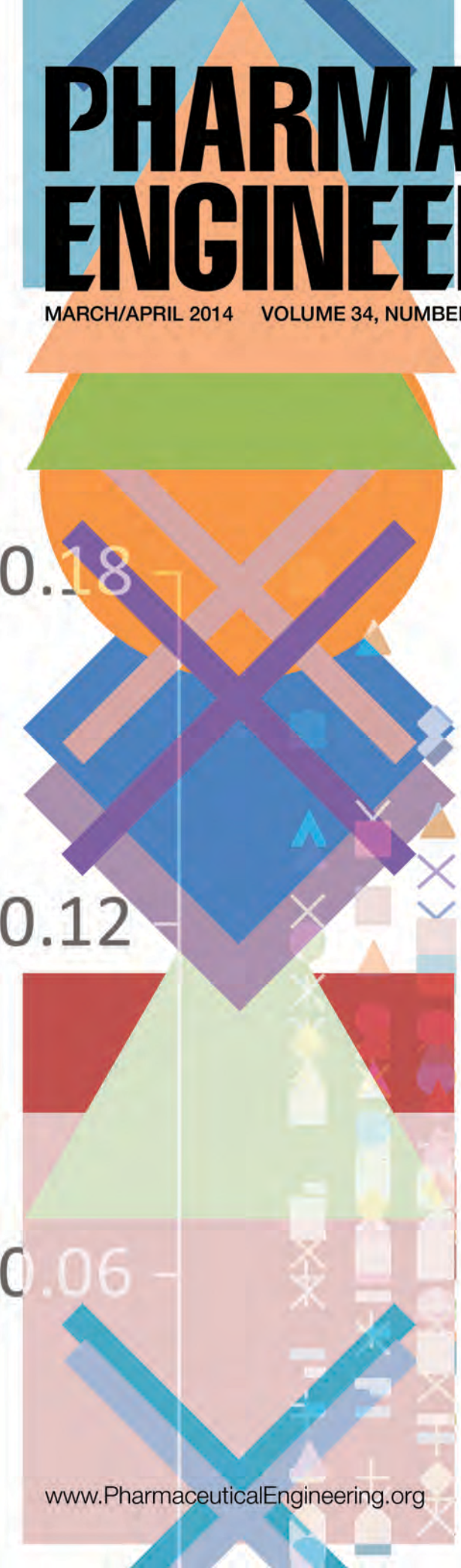
PHARMACEUTICAL ENGINEERING®

THE OFFICIAL TECHNICAL MAGAZINE OF ISPE

MARCH/APRIL 2014 VOLUME 34, NUMBER 2

Pharmaceutical Quality Management
Risk-Based Management Processes
Stratified Sampling
Project Execution Planning
Contamination Risk Reduction
Regulatory Harmonization
Clean Design
On-Line TOC Monitoring



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ISPE Global Headquarters
600 N. Westshore Blvd.
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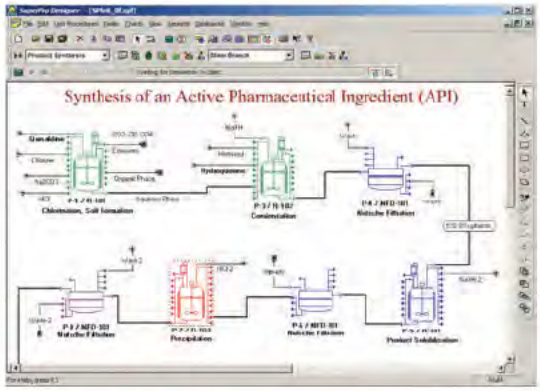

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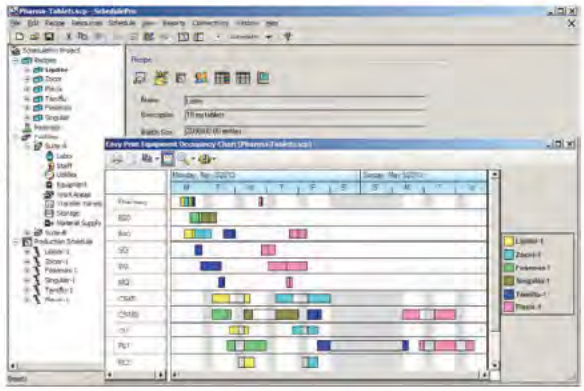

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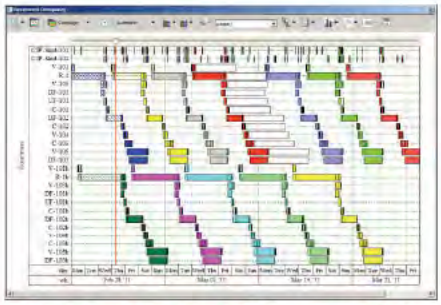

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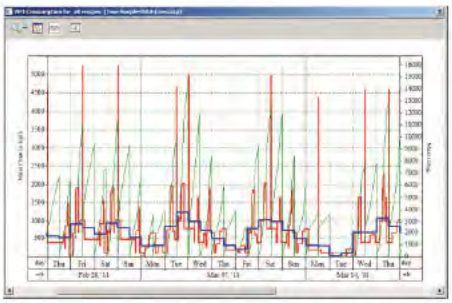

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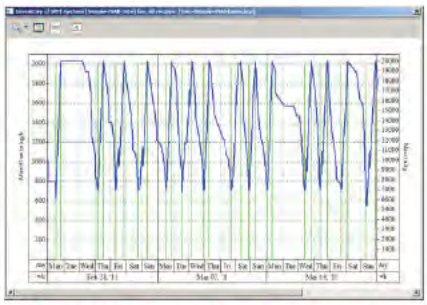

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Concept to Operation: Performance and Reliability

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Welcome to this edition of *Pharmaceutical Engineering*, which touches on many key aspects of an effective pharmaceutical quality system, concerned with enabling innovation, productivity, and profitability as well as quality, cleanliness, and compliance, and of course ensuring the ethical responsibility to the patient: the person at the end of the supply chain.

Wingate discusses a collective challenge facing the industry today in his article "Moving from Quality Control to Quality Assurance." Proactive compliance entails creating or controlling a situation rather than just responding to it after it has happened, and achieving sustained higher performance (often during a period of significant change) while still safeguarding compliance and product quality. The article reminds us that quality leadership and culture must come from the top, and that we must never compromise the GMP fundamentals.

The accuracy and integrity of tests and measurement depend on the fitness for purpose of instruments and systems used. Rattan and Rubacha present a compliant and practical risk-based validation process for laboratory systems. The biologics analytical department at Bristol-Myers Squibb have created and implemented an eight-step process to manage risk in systems as simple as pH meters and as complex as HPLC systems. To date 412 risk assessments have been completed.

The article by Garcia, et al, discusses the concerns that led to the withdrawal of the FDA draft guidance for industry, "Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment," and potential alternative approaches for the assessment of blend and content uniformity of solid dosage forms.

Garner explains the importance of a Project Execution Plan (PEP) for a pharmaceutical facilities project and outlines the fundamental aspects of a PEP and what should be included.

In "Contamination Risk Reduction within Ongoing Operations," Hammond and Van Wormer discuss how the development and utilization of good construction practices can help prevent product safety issues in existing pharmaceutical facilities.

Henon, et al, describe the harmonization of American Society of Mechanical Engineers (ASME) codes and standards in the area of high purity process piping. This is a great example of how volunteers from different committees can work together to improve standards with benefit to both industry and society.

In "The Dirt on Cleaning and Sanitization," Lewis and Shank give us a comprehensive overview of the basic concepts and principles of clean design which should be applied when considering equipment and system design. The authors remind us, in words attributed to Benjamin Franklin, that *"In wine there is wisdom, in beer there is freedom, and in water there is bacteria!"*

Total Organic Carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon, and is often used as a non-specific indicator of water quality or cleanliness of pharmaceutical manufacturing equipment. Dion, et al, present a TOC monitoring system integrated into a GMP parts washer and discusses how it can increase productivity, help meet PAT and QbD goals, and provide ongoing assurance over the life cycle of the process.

Over the past 18 months, we have implemented a series of editorial and style changes in *Pharmaceutical Engineering*. Our goal is to continue to improve PE's editorial content and accessibility so that it remains a valued member benefit, dependable industry resource, and trusted technical source. To gauge your interest in PE's editorial strategy, future delivery and format preferences, and industry relevance, we are conducting a series of readership surveys. Look for the first one with the digital edition of this issue.

I am also excited to announce that ISPE has launched its official blog, ISPEAK, that will feature perspectives from Members, guest authors, volunteers and staff on industry hot topics and Society news. Check it out on the ISPE homepage and send your content ideas and contributions to Ispeak@ispe.org.

As always, I welcome your feedback – email me at ghall@ispe.org.

Gloria Hall
Editor, *Pharmaceutical Engineering*

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Spanning the Globe and Making a Difference

Berg discusses how ISPE is stimulating new approaches, leading change in how business is conducted and influencing how regulations are being developed through global regulatory interaction.

Thanks to you, ISPE is a vital resource to health authorities. Together, we are changing the way products are developed and produced, improving quality and enhancing practices that were once thought unchangeable. The Society is making a difference because of our Members who comprise a neutral technical expert network that is unmatched in any group, any company or any other association. "Team ISPE" is highly respected and a valued resource. As a Member of the Society, **YOU** are part of that team that is stimulating new approaches, leading change in how business is conducted—and frankly, how regulations are developed. We appreciate the many contributions that Members made to technical and regulatory discussions in 2013. Last year, ISPE submitted comments on a record number of proposed regulations and guidances and we initiated or extended dialogue on major issues such as drug shortages—just one of many active topics with regulators.

ISPE continues to build on the work of the 2013 Drug Shortages Survey. Last October, ISPE presented as an invited guest at EMA's London workshop on product shortages. Following that workshop, ISPE has facilitated a multi-association task force on this topic and in January, this task force presented EMA with a proposal and plan addressing the prevention of drug shortages due to manufacturing quality issues. The task force will continue working on this plan and incorporate feedback from EMA.

In February, ISPE leaders and I updated the FDA on ISPE's Drug Shortages Initiative (now global with the addition of the abovementioned EMA project). This discussion responded to an FDA request for information on average approval timelines relating to aseptic facilities updates. We also met with representatives from MHLW (Japan) to discuss technical issues—one of many discussions around global approaches to problem-solving and opportunities for harmonized approaches.

ISPE's Quality Metrics Working Group completed a significant white paper earlier this year. This paper encompassed feedback from in-depth discussions with Members and their companies at ISPE workshops. This group continues further developing its approach to the topic, working closely with the FDA.

ISPE is an important link between industry and regulators and your participation at ISPE conferences not only enhances your knowledge but "being there" offers opportunities to learn from and communicate with regulators. ISPE's Europe Annual Conference (28-30 April, Frankfurt, Germany) will feature key regulators from EMA, MHRA and national regulatory agencies of Germany, Netherlands and other European countries. The 3rd Annual ISPE-FDA CGMP Conference (2-4 June, Baltimore, MD) includes in-depth discussions on data integrity, new compliance approaches, quality systems and other leading topics. This year's CGMP Conference will host ISPE's "Pharmaceutical Quality Week" to recognize the important contributions by Members and our industry. This special "week" also includes an Executive CMO Workshop and the ISPE Facility of the Year Awards 10th Anniversary Gala honoring past recipients and the 2014 category winners.

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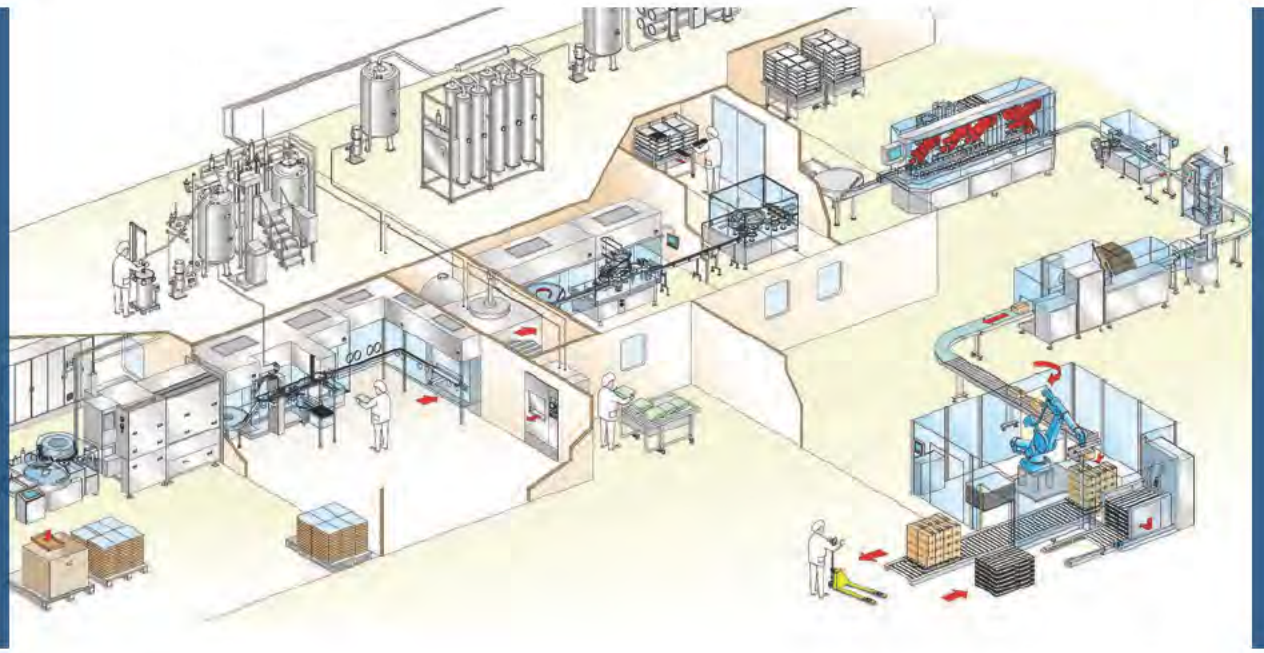

Moving from Quality Control to Quality Assurance

by Guy Wingate, PhD

This article provides ways to implement an effective quality management system to allow manufacturers to meet their ethical and regulatory obligations.

This article is based on content from the presentation, "Moving from Quality Control to Quality Assurance" held during the ISPE Proactive Compliance Conference on 13-14 January 2014 by Dr. Guy Wingate, VP and Compliance Officer (Global Manufacturing and Supply), GSK. As reflected in the theme of the conference, a collective challenge facing the industry is to achieve proactive compliance. This involves effective management and control of the manufacturing environment to avoid problems rather than just responding to problems after they have happened.

As it applies to many of us, this means assuring sustained higher performance (often during a period of significant change) with no nasty surprises. Central to our thinking must be the person at the end of our supply chain and their trust in us to comply with regulatory requirements and ensure the products we make are fit for purpose. In the pharmaceutical industry, the Quality Department is playing an increasingly pivotal role in running a sustainably profitable business that is also committed to meeting the expectations of the patient and the public. Executive managers, R&D, manufacturing, and sales and marketing all feel the pressures of productivity challenges, organizational changes and increasing regulatory requirements, but the fundamentals of quality and compliance must never be compromised. The implementation of an effective quality management system allows manufacturers to meet their ethical and regulatory obligations. It is good business sense to remove defects, reduce deviations and eliminate waste. To achieve the highest level of safety, purity, and efficacy of drug products, quality management teams are moving beyond Quality Control (QC) and into Quality Assurance (QA).[1,2] Today's modern businesses are becoming more proactive and less reactive.[3]

The World Health Organization defines Quality Control (QC) as "the sum of all procedures undertaken to ensure the identity and purity of a particular pharmaceutical."[3] The purpose of QC is to ensure the safety and efficacy of a finished drug product before it is released to the public. Supporting quality systems need to detect whether items such as raw materials, components, containers, labeling and packaging fail to meet pre-existing specifications. The QC Department is responsible for conducting this work as well as testing the finished product to ensure it meets regulatory requirements. For pharmaceuticals, QC may involve analytical procedures ranging from simple substance screenings to complex pharmacopoeia monographs.

Quality control at its core is a reactive process. The premarket checks and inspections do their best to assure phar-

Quality Control vs. Quality Assurance	
Quality Control	**Quality Assurance**
Product	Process
Reactive	Proactive
Corrective tool	Preventative tool
Completed by experts	Implemented by managers
Ensures and checks	Develops and defines
Failure detection	Failure prevention
Identify and correct defects	Prevents defects
Identification through inspections and peer review	Prevention with statistical and managerial tools

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maceutical manufacturers of the standard of products being made and sold, but QC alone cannot guarantee that a high quality product will be consistently produced. Substantial manufacturing waste (time and materials as a result of process deviations) and post-market recalls are evidence of this. A better approach is needed as the FDA acknowledge in their 2006 Guidance for Industry, Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations stated, "Quality should be built into the product, and testing alone cannot be relied on to ensure product quality."[4]

Quality Assurance (QA) involves taking a proactive approach to ensure drug products are made in accordance with manufacturing standards and met their pre-defined product specifications. The aim is for quality and compliance to be achieved "right the first time" rather than depend on detecting problems. The aim is to continually improve manufacturing standards, eliminating errors along the way. Quality control still has a role to play, but with effective QA and reliable operational performance during the process, it becomes a component of the pharmaceutical quality system.[2]

The responsibilities of quality assurance include:

- Products intended for public are safe, effective, and appropriate as to dosage.
- Predetermined quality standards are upheld when choosing and accepting products from suppliers.
- Labeling and packaging meets regulatory requirements as to storage and usage.
- Recall process is standardized and prepared for defects in post-market products.
- Post-market communications are available for public concerns and questions.

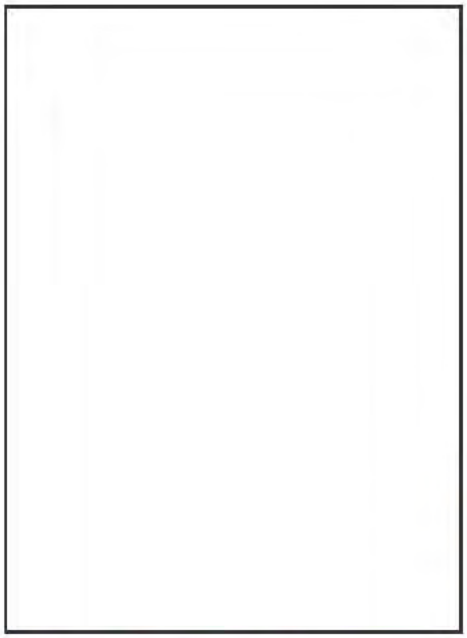
The leading guidance on pharmaceutical quality management systems is ICH Q10 published in 2009 by the International Conference on Harmonisation (ICH). This Guide describes quality system management integrating Good Manufacturing Practice (GMP), based on science- and risk-based approaches.[1] Quality assurance is a part (along with quality control) of the broader concept of quality management. Pharmaceutical quality systems need to provide the necessary framework for implementing continual improvement and risk management in the drug manufacturing process.[4] This is also consistent with the concepts of Quality by Design (QbD).[5]

A holistic approach to quality assurance is needed. The internal control framework needs to cover governance, systems and processes, as well as distinct activities that encourage a supportive mindset and organizational behavior. Key aspects to consider include:

- Company Awareness – quality assurance is a part of normal business, an integral part of achieving long and short-term goals. Success depends on total commitment of management and staff.
- Product Knowledge – quality assurance must have complete documented product, system, and process knowledge. Product knowledge must include raw material and specific production audit, testing, and validation requirements.
- Facility Knowledge – quality teams should include personnel with expertise of equipment and access to educational resources to stay current with regulatory updates and process validation changes.
- Basic GMPs – ensure basic cGMP compliance is robust and sustained (in place, in use and effective). Never assume basic processes like deviation management, root cause analysis and Corrective and Preventive Action (CAPA) look after themselves. CGMP compliance is perishable and needs nurturing to support quality assurance.
- Networking – quality assurance teams should be proactive in networking with regulatory agencies and peers with similar product lines. Opportunities should be made available for education and current trends through conferences and regulatory resources.
- Risk Analyses and Decision Allowances – risk analyses should be based on good science and data. Decision making authority should be backed with expert process analyses and the ability to alter standard operating procedures.[6]

> *"The holistic approach to quality assurance needs to promote transparency in support of performance improvement.*

Pharmaceutical companies must ensure they do not fall down on the basics. A good example was discussed at the ISPE Proactive Compliance event. Management often use a single metric to track the effectiveness of CAPA management. The chosen metric can have unforeseen implications if it focuses on the corrective aspect of CAPA to return a process to normal operation. CAPA actually comprises two distinct activities as the name suggests. The first aspect focuses on investigating, understanding, and taking action to correct a problem. The second aspect focuses on defining and implementing action to prevent recurrence. Fundamental to both, in order to achieve successful quality performance improvement, is the identification of the real root cause of the problem being fixed and not to rely or accept cursory or superficial assessments based on assumptions. A separate



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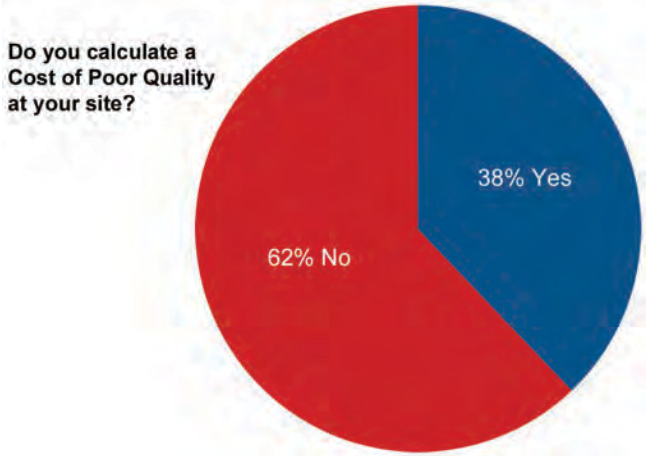

Figure 1. Calculating cost of poor quality at your site (ISPE/PDA Survey September 2011).

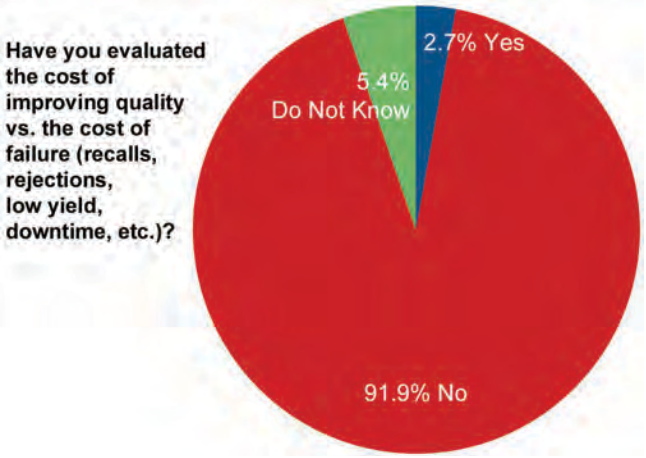

Figure 2. Evaluating the cost of improving quality (ISPE/PDA Survey September 2011).

metric for each aspect of CAPA is therefore recommended which require equal management attention.

The holistic approach to quality assurance needs to promote transparency in support of performance improvement. Staff, wherever they work, need to feel safe in raising deviations and other concerns with their line management. An open and trusting relationship must be maintained so that production problems are raised as they occur for rapid resolution. A learning culture needs to replace a "mistakes-are-punished" or a "someone-is-to-blame" approach to quality issues. A Speak-Up program should be established to provide an alternative means for staff to raise concerns to an internal independent group. Such programs need to make provision that enable confidential disclosures to be made. It is vital to sustain trust and prevent any retaliation against those raising problems in good faith. It is better for organizations to deal promptly with issues raised than wait for a frustrated individual to feel their only option is to become a whistleblower.

Although companies are finding the value in moving toward the QA paradigm, reaching optimal quality assurance has its challenges. Quality systems in manufacturing sites are often hindered by cumbersome collections of documents requiring reactive rewrites with process or procedural changes. Manufacturers also face a lack of Subject Matter Experts (SMEs) with the necessary process and product understanding to support leading edge practices such as Quality by Design (QbD) and Quality Risk Management (QRM). Pharmaceutical manufacturing companies need to lead the manufacturing industry by committing to enhanced QA by eliminating inefficient processes and streamlining manufacturing operations.

In 2012, Richard Friedman, Associate Director of FDA's CDER's Compliance Office's Office of Product Quality, addressed the need for pharmaceutical companies to modernize the control process in which products are manufactured and better analyze the quality risks. This direction is supported by Generic Drug User Fee Program and the FDA Safety and Innovation Act. Friedman endorsed the intent of ICH Q10 which is optimal quality through knowledge management, change, and innovation.[7] Pharmaceutical quality management teams can modernize manufacturing by constructing their quality system on a holistic framework of key elements. Governing management, system processes, and a quality culture mindset become the basis of quality management, and therefore, quality assurance. Within this structure, elements such as QbD and QRM support each

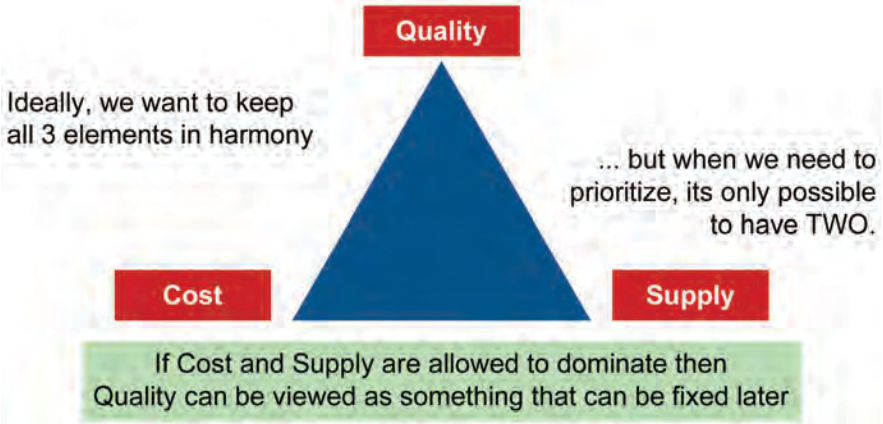

Figure 3. Ghost in the Machine – Culture.

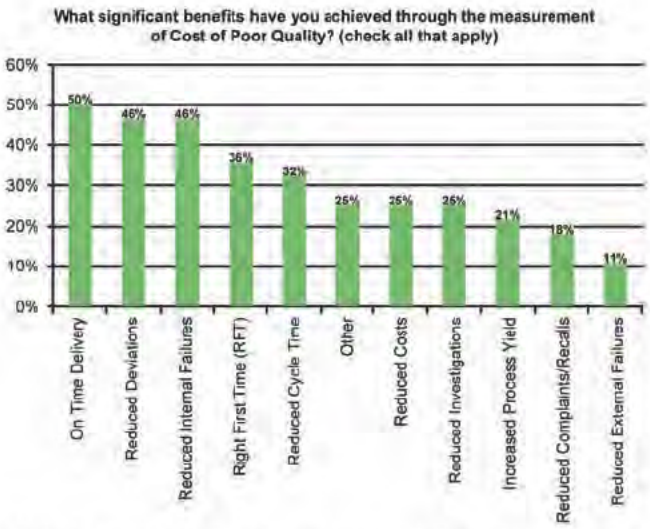

Figure 4. Significant benefits achieved through the measurement of cost of poor quality.

other. This facilitates sustained and continual improvement benefiting both patients and business stakeholders.

Quality can be better managed when it is recognized and understood that the control of variability and prevention of waste is imperative to achieve a cost effective business[8] - *Figure 1.* In 2011, an ISPE/PDA joint survey found that more than half of manufacturers had not calculated or evaluated the projected outcomes of the Cost of Poor Quality (CPQ) - *Figure 2.* Ideally, we strive to keep quality, cost, and supply in harmony, but when we need to prioritize, it is only possible to achieve two and quality must always be preserved - *Figure 3.* Quality management when structured with quality assurance using cost analyses as a business driver, reaps the cost benefits of a proactive approach - *Figure 4.*

A company must set the "tone from the top" when raising expectations of quality by implementing a systematic quality management approach. To move into quality assurance and therefore a more proactive approach to quality, senior managers must first understand the specific working principles of the site including its drivers, constraints, and manufacturing goals. Taking these points into account, management must then strategically prioritize cost targets, quality expectations, and their business scope.[2]

The U.S. Department of Justice has set out clear expectations for company executives senior management when it comes to cGMP compliance.[9] The following reflective questions give an indication of what is expected from company leaders.

- Do we have the right people (capability and attitude – employees, contractors, suppliers)?
- Do people have the right incentives to see, report and fix problems?
- Are people satisfied and engaged?
- Do policies and procedures acknowledge how real people work and what they are capable of?
- Do managers have personal visibility into what people are actually doing?
- Is there a supportive organisational culture in place?

Individuals can find themselves culpable for not taking these expectations seriously.

Management must clearly communicate what needs to be accomplished so that everyone understands what is expected. Part of this should include explaining what is not tolerated in terms of standards and behavior. The same expectations should be applied equally, including any supporting disciplinary processes, to all levels of the organization.

To achieve higher quality through QA, manufacturing companies, as well as suppliers and regulators must work together. FDA Commissioner Janet Woodcock recommends an investment in the mutual objective of "an agile, flexible pharmaceutical manufacturing sector that can reliably produce high quality medicines without extensive regulatory oversight."[10] Shared beliefs, values, attitudes, and behavior patterns are pieces of the jigsaw that must come together.

> *"Adopting a proactive approach to quality management is essential to achieve the step change in quality performance expected from our industry.*

Adopting a proactive approach to quality management is essential to achieve the step change in quality performance expected from our industry. The energy and motivation for quality comes from the top. Management must acknowledge the challenge of change this will involve in their organizations and stay vigilant. Everyone must play their part. A culture of quality will empower teams to continually improve and solve problems. We must remember that the person at the end of our supply chain is depending on us to provide safe and effective medicines.

**Disclamer: the views expressed are personal opinions and do not necessarily represent the views of GlaxoSmithKline.*

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About the Author

Guy Wingate, PhD is currently Vice-President and Compliance Officer for Global Manufacturing and Supply at GlaxoSmithKline and has more than 20 years of experience working in the pharmaceutical industry. At GSK he has held several roles including overall responsibility for quality for one of GSK's largest manufacturing sites, responsibility for QA technology strategy, leading a major revision to the GSK corporate quality management system, and overall responsibility for computer compliance standards and implementation. Wingate has been involved with the GAMP COP for 21 years in various capacities; most recently he has chaired its governing body GAMP Council 2000-2010. He has led the Task Teams producing several ISPE guidance documents, including GAMP® 5 and the Science and Risk-based Approach for the Delivery of Facilities, Systems, and Equipment Guide. Wingate served on the ISPE International Board of Directors between 2008-2012. He is a Chartered Engineer and holds a BSc, MSc, and PhD from University of Durham in computing, advanced electronics, and engineering science respectively. He is widely published in journals and books, and regularly chairs and speaks at conferences in the US and Europe. He can be contacted by email: guy.as.wingate@gsk.com.

GlaxoSmithKline, C Block Main Office Harmine Rd., Barnard Castle, County Durham, United Kingdom DL 12 8DT.

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Applying a Consistent, Compliant, and Practical Risk-Based Validation Process for Laboratory Systems

by Anil K. Rattan, PhD and Michael Rubacha

This article presents a consistent, compliant and practical risk-based validation process for laboratory systems.

Scientific and Risk-Based Management (RBM) processes for laboratory systems have been suggested in several pharmaceutical guidelines[1, 2, 3] and as a result, various RBM processes have been applied in the industry. Most implementations result in some customization of the guidelines since no comprehensive plan is identified and guidelines are open to interpretation. This article serves to close that gap by offering a consistent, compliant, and practical RBM validation process for laboratory systems.

Over the last three years, the biologics analytical department at Bristol-Myers Squibb created and implemented an eight-step process (Figure 1) to manage risk in systems as simple as pH meters and as complex as HPLC systems. To date, 412 risk assessments have been completed. By following these steps, any pharmaceutical company can implement a program that determines system impact, asset protection recommendations, regulatory risk, record vulnerability, system complexity, criticality, and documentation deliverables. This approach is consistent and provides cost savings from leveraging previous validation documents.

Introduction

In 2008, the International Society for Pharmaceutical Engineering (ISPE) published its Good Automated Manufacturing Practice document, version 5 (GAMP® 5) entitled, "A Risk-Based Approach to Compliant GxP Computerized

Figure 1. Eight step process workflow.

Systems."[1] GAMP® 5 is used by the pharmaceutical industry to provide guidance for managing regulated systems. Unfortunately, this guide lacks the granularity needed to assist companies in designing their own tools for RBM of laboratory systems.

Although it lacks granularity, GAMP® 5 provides a foundation upon which a risk-based approach can be built. According to GAMP® 5, risk management should focus on patient safety, product quality, and data integrity.[1] It also suggests documentation and activities required to provide a high degree of assurance that each laboratory system is properly regulated. Also, GAMP® 5 is clear that risk management should cover the entire lifecycle of the system. While these points are elucidated in GAMP® 5, no concrete examples or tools are provided.

Question:	Response?	Instructions:
1. Does the system have a direct impact on patient safety, product quality and data integrity?	☐ Yes ☐ No	If Yes, classify the system as "Direct Impact," select No for Question 2, and go to Step 2.
2. Does the system have an indirect impact on patient safety, product quality and data integrity?	☐ Yes ☐ No	If Yes, classify the system as "Indirect Impact," and go to Step 2. Otherwise, classify the system as "No Impact Non-GxP" and stop.
Classification:	☐ Direct Impact ☐ Indirect Impact ☐ No Impact Non-GxP	

Table A. System impact.

In conjunction with GAMP® 5, the International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use also discusses quality risk management.[2,4,5,6] In its documentation, ICH explains that risk management should systematically identify and analyze hazards associated with the use of systems. While this dictum is given, the same gap apparent with GAMP® 5 is found in the ICH documentation. Namely, no concrete examples or tools are provided.

In harmony with GAMP® 5 and ICH, the Parenteral Drug Association published two technical reports in 2012 discussing the quality risk management for pharmaceutical and biotechnology operations in a phase appropriate manner.[7,8] Various other publications and guidelines exist on the topic as well, such as the European Commission's EudraLex,[3] the

Statement:	Response?	Instructions:
1. System is a web application.	☐ Yes ☐ No	If Yes, Deliverable 1 is applicable.
2. System is a mobile device (e.g. iPhone, BlackBerry, PDA).	☐ Yes ☐ No	If Yes, Deliverable 2 is applicable.
3. System connects to other application(s).	☐ Yes ☐ No	If Yes, Deliverable 3 is applicable.
4. System includes infrastructure components (e.g. database, server).	☐ Yes ☐ No	If Yes, Deliverable 4 is applicable.
5. System requires an account administrator.	☐ Yes ☐ No	If Yes, Deliverable 5 is applicable.
6. System makes use of user ID and password.*	☐ Yes ☐ No	If Yes, Deliverable 6 is applicable.
7. None of the above statements are applicable.	☐ Yes ☐ No	If Yes, Deliverable 7 is applicable.
*Note: The use of unique user ID and password (Item No. 6, Table B) is only applicable if the system maintains regulated electronic records and signatures based on FDA 21 CFR Part 11.		

Table B. Asset protection assessment.

Pharmaceutical Inspection Co-operation Scheme (PIC/S),[9] and Heath Canada and PHAC's Integrated Risk Management.[10]

These guidelines and technical reports, while vital for industry knowledge, suffer the same malady as the others: a lack of granularity needed to fully implement a consistent, compliant, and practical RBM validation process for laboratory systems. Recently, another GAMP® Good Practice Guide was published[11] regarding the validation of laboratory computerized systems. In this guide, it is clearly stated that "due to the wide diversity of systems, a single prescriptive approach would be neither practical nor cost-effective." However, the approach discussed in this article has been successful for both non-GxP and GxP systems within a Biologics Analytical Development and Testing (BAD&T) group. The more complicated computerized systems such as LIMS, SAP, and other enterprise systems were out of scope for this process.

In order to mitigate these gaps, and begin to discuss, in detail, a proposed process for managing risk, Bristol-Myers Squibb's BAD&T department researched a plethora of guidelines and technical reports available on the topic. Leveraging these documents, the following can be said about RBM:

Risk-based management is the systematic accumulation of, and ongoing knowledge about the potential and actual hazards associated with the operation and maintenance of a system in order to control and reduce risk throughout its lifecycle.

The Model

Based on this definition for RBM and considerations for practical implementation, an eight-step process was developed and employed. The first seven steps are used to determine deliverables in the Project Phase, while the eighth step is used to determine deliverables in the Operations Phase. The eight steps are shown in the Figure 1.

Step 1: Determine the System Impact

When considering system impact, the chief concern is the risk to product quality. System impact on product quality is determined by answering two questions as seen in Table A. In answering these two questions, a determination can be made as to whether the system has a direct, indirect, or no impact on product quality. A direct impact system is one that is typically used in manufacturing or produces data that are used to make decisions concerning the manufacturing process.

An indirect system is one that is not used in manufacturing and does not produce data used to make manufacturing decisions, but supports direct impact systems. The term "support" provides a

Deliverable:	Instructions:
1. Complete an Application Vulnerability Assessment (not included in this article) on the current version, determine if "https" needs to be used, and whether it is used on the entire website, and test accordingly.	Go to Step 3.
2. Test that unencrypted highly confidential information is deleted and not stored, ensure software security updates are kept current, configure to prompt users for PIN or strong password when turned on, ensure PIN or password cannot be auto-saved.	Go to Step 3.
3. Ensure access is granted based on target audience; develop a periodic review to be performed on a systematic basis (i.e. every x number of years).	Go to Step 3.
4. Perform tests to scan all infrastructure components.	Go to Step 3.
5. Establish an Access Model (not included in this article).	Go to Step 3.
6. Test against the applicable sections of the FDA's 21 CFR Part 11.	Go to Step 3.
7. Document that decision that no asset protection is required.	Go to Step 3.

Table C. Asset protection deliverables

broad interpretation and covers systems that produce data used in various documents, such as batch filings, master batch records, and regulatory submissions.

A no impact system is one that has neither direct nor indirect impact on product quality. This type of system is also considered non-GxP. If a system is considered no-impact non-GxP, the rest of the eight-step process is not applicable. In this case, the example will be any local or stand alone system in a development lab which is used only for research purposes such as pH meters, balances, plate readers, etc.

Step 2: Decide the Asset Protection Deliverables

Asset protection deliverables vary based on the type and complexity of the system. Table B lists some of the considerations taken into account when deciding which deliverables to execute in Table C. The list of statements provided in Table B is an abbreviated list and can be built upon as determined by individual company needs. Questions which are considered Bristol-Myers Squibb specific were left off the list.

Answering "Yes" to one or many of the statements in Table B corresponds to action items in Table C. For example, if the system is a mobile device (Statement 2, Table B), a myriad of action items are required (Deliverable 2, Table C) including PIN or strong password testing, deletion of unencrypted highly confidential information, and regular software security updates.

If the system makes use of user ID and password (Statement 6, Table B), the applicable sections of the FDA's 21 CFR Part 11 should be tested against (Deliverable 6, Table C). If none of the statements in Table B apply to the system, no asset protection is required (Deliverable 7, Table C).

Step 3: Assess the Regulatory Risk

Potential system usage is paramount when assessing regulatory risk. Table D lists questions that should be asked when determining if a system poses a high or low regulatory risk. The level of regulatory risk is combined with the level of record vulnerability (Step 4) to determine the overall system risk.

A high risk designation should be given to any system that meets at least one of the criteria for potential system use provided in Table D. If none of the potential system uses are

Potential System Use:	Response?	Instructions:
1. System has a direct impact on product quality.	☐ Yes ☐ No	If Yes, assign a high risk.
2. Missing, incomplete, or changed data generated by the system makes it impossible to reproduce the decision process that led to decision or action.	☐ Yes ☐ No	If Yes, assign a high risk.
3. Data are submitted to regulatory agencies.	☐ Yes ☐ No	If Yes, assign a high risk.
4. Produces data supporting batch release.	☐ Yes ☐ No	If Yes, assign a high risk.
5. Produces stability data for drug product.	☐ Yes ☐ No	If Yes, assign a high risk.
6. Receives data from or produces data to support clinical laboratory studies.	☐ Yes ☐ No	If Yes, assign a high risk.
Regulatory Risk:	☐ High ☐ Low	

Table D. Assess the regulatory risk.

System Nature:	Response?	Instructions:
1. System is considered custom built, or includes a custom modification to an existing application.	☐ Yes ☐ No	If Yes, assign a high risk.
2. System is a commercially available package that involves configuring predefined software modules and possibly developing customized modules.	☐ Yes ☐ No	If Yes, assign a high risk.
Record Vulnerability:	☐ High ☐ Low	

Table E. Assess the record vulnerability.

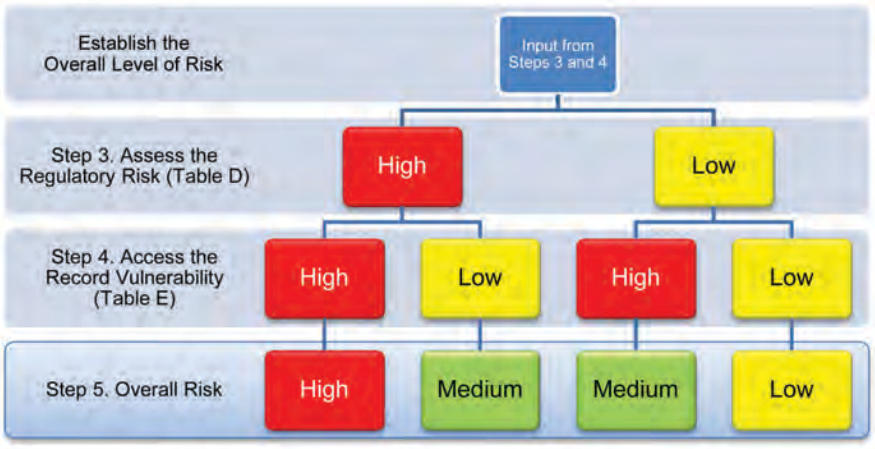

Figure 2. Risk assessment workflow.

System Complexity:	Response?
1. System produces data.	☐ Yes ☐ No
2. System data reside on a server.	☐ Yes ☐ No
3. System uses computer interface.	☐ Yes ☐ No
4. System uses instrument interface or is an instrument itself.	☐ Yes ☐ No

Table F. System complexity

Response 1	Response 2	Response 3	Response 4	Category
Yes	Yes	Yes	Yes	☐ A
Yes	Yes	Yes	No	☐ B
Yes	No	Yes	Yes	☐ C
Yes	No	Yes	No	☐ D
Yes	No	No	Yes	☐ E
No	No	No	Yes	☐ F

Table G. System category.

applicable to the system, a low risk designation should be assigned. Additional usage criteria can be included in Table D based on individual company requirements.

Step 4: Assess the Record Vulnerability

Record vulnerability is determined by examining the system nature. Systems that are considered commercial off-the-shelf inherently have a lower record vulnerability (provided the proper quality controls are in place from the manufacturer). Therefore, the important considerations when assessing record vulnerability revolve around the level of customization proposed for the system.

Table E provides two such statements regarding customization. A high vulnerability should be assigned if either of the two statements is applicable to the system. If neither of the two statements is applicable, the system is considered commercial off-the-shelf and given a low vulnerability rating.

Step 5: Establish the Overall Level of Risk

The overall level of risk is established from a review of the outcomes in Steps 3 and 4. A high regulatory risk (Step 3) and a high record vulnerability (Step 4) result in a high overall risk - *Figure 2*. On the opposite side of the spectrum, a low regulatory risk and a low record vulnerability result in a low overall risk. Alternatively, a low/high risk mix between Steps 3 and 4 result in a medium overall risk. Overall system risk is used in conjunction with the assessment of system complexity (Step 6) to provide the list of recommended documentation and testing needed for validation (Step 7).

Step 6: Assess the System Complexity

Once overall risk is established (high, medium, or low), the next step is to assess the system complexity. Assessing complexity provides further granularity when determining documentation deliverables. For example, a high risk client-server system and a high risk stand alone instrument should not have the same level of documentation deliverables. Because of this, a series of system complexity questions were developed to determine the proper categorization - *Table F.*

Depending on the combination of responses to the statements in Table F one category, A through E, is assigned using Table G. Category A systems are the most complex with client-server build and instrument interactions. A Category A system is one in which each system complexity statement is answered in the affirmative. Progressing through Category F, the systems become less complex. A Category F system is one in which only the final system complexity statement is answered in the affirmative. A summary of the categories is provided in Table H.

Client-Server System		Local System		Stand Alone System	
A	B	C	D	E	F
Data Produced	Data Produced	Data Produced	Data Produced	Data Produced	No Data Produced
Data Can Reside on Server	Data Can Reside On Server	Data Reside on Local PC	Data Reside on Local PC	No Data on Server/PC	No Data on Server/PC
PC Interface	PC Interface	PC Interface	PC Interface	No PC Interface	No PC Interface
Instrument Interface	No Instrument Interface	Instrument Interface	No Instrument Interface	Is an Instrument	Is an Instrument
Note: This approach is only used for local and stand alone systems in the BAD&T group. The client-server based systems and all the enterprise systems were out of scope using these guidelines such as categories A and B.					

Table H. Summary of system categories.

Step 7: Decide the Documentation Deliverables

As a culmination to the first six steps, Step 7 combines overall risk and system complexity to decide documentation deliverables for the Project Phase - *Table I*. Completion of these deliverables provides a high degree of assurance that the system is validated. The matrix in Table I lists the applicability of each deliverable

	☐ High						☐ Medium						☐ Low					
	☐ A	☐ B	☐ C	☐ D	☐ E	☐ F	☐ A	☐ B	☐ C	☐ D	☐ E	☐ F	☐ A	☐ B	☐ C	☐ D	☐ E	☐ F
Requirements/Traceability	X	X	X	X	X	X	X	X	X	X								
Design Specification	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Quality Assessment	X	X	X	X	X	X	X	X	X	X								
Validation Plan	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Installation Qualification	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Operational Qualification	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance Qualification	X	X	X	X	X	X	X	X	X	X	X	X						
21 CFR Part 11 Testing*	X	X	X	X			X	X	X	X								
Acceptance Testing	X	X	X	X	X	X	X	X	X	X	X	X						
Validation Report	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Note: This approach is only used for local and stand alone systems in the BAD&T group. The client-server based systems and all the enterprise systems were out of scope using these guidelines such as categories A and B. The FDA 21 CFR Part 11 testing can be performed based on the risk and complexity of the system but we took a conservative approach and performed this task on most of our systems.

Table I. Project phase validation documentation deliverables.

across the different levels of risk and system complexity (Xs are applicable).

For example, a system that is determined to be low risk, Category E, (e.g., most laboratory balances) would require installation qualification and operational qualification. Whereas, a medium risk, Category C system (e.g., HPLC) would require all the listed deliverables. It should be noted that although the deliverables listed for all medium to high risk Category A-D systems are identical, the testing scrutiny and documentation sections vary.

Step 8: Determine the GxP Criticality

While Steps 1 through Step 7 are a risk-based approach used for the Project Phase validation, Step 8 is a risk-based approach for the Operations Phase. As mentioned previously, the BMS biologics definition for laboratory systems risk management encompasses the entire system lifecycle. Therefore, GxP criticality also must be determined. The level of GxP criticality will affect maintenance and quality decisions. Aspects such as the frequency of calibration, and whether to launch quality investigations for system failures are determined based on the GxP criticality.

An example set of questions in Table J is provided. More questions may be added based on company-specific needs. Based on these questions, there are two possible outcomes. The system can be labeled: GxP Critical or GxP Non-Critical. If any of the questions are answered "Yes," the system is GxP Critical. If none of the questions are answered "Yes," the system is GxP Non-Critical. A GxP Critical system may require a higher frequency of calibrations throughout the year, and a failure during calibration would launch a quality investigation. The full extent of the requirements for a critical vs. non-critical system should be determined in cooperation with quality personnel.

Conclusion

While the industry continues to wrestle with implementing risk management in ways that reliably fulfill both the letter of the regulatory guidelines as well as their intentions; this eight-step process has consistently met the needs of the Bristol-Myers Squibb BAD&T organization. As a result, this process will be scaled to include the process sciences division of the organization; a four-fold growth in systems under the scope. After having used and refined the process for

System Use:	Response?	Comments
1. Does the system monitor critical process parameters?	☐ Yes ☐ No	If Yes, label the system GxP Critical.
2. Will a failure impact product quality or not be detected by another system?	☐ Yes ☐ No	If Yes, label the system GxP Critical.
3. Is information from the system required for a manufacturing batch record?	☐ Yes ☐ No	If Yes, label the system GxP Critical.
If all three questions were No, label the system GxP Non-Critical.		

Table J. GxP criticality.

three years, there is confidence that these eight steps truly do provide a consistent, compliant, and practical RBM for laboratory systems.

The main advantages of this process are: consistency in our approach from system to system, shortened time to author and complete validations, and fast quality approval due to consistent contents. A disadvantage of using this process is that it isn't robust for more complex systems such as LIMS, SAP, or any enterprise applications.

It is important to remember that any process should continually be refined. Based on the latest "A Risk-Based Approach to GxP Compliant Laboratory Computerized Systems,"[11] we will modify the appropriate steps to make this process more robust, consistent, compliant and practical for our use in the future.

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About the Authors

Anil K. Rattan holds a PhD in biology with a specialization in animal neurosciences from Guru Nanak Dev University in Punjab, India. For his post-doctorate, Dr Rattan attended Ohio State University. After his studies, he worked as a research scientist at NYU Medical Center and at Saint Francis Hospital. In 1998, he joined Wyeth as a senior information scientist, and then joined Bristol-Myers Squibb (BMS) in 2002 as a senior manager in their Analytical Department. For the last 12 years, Dr. Rattan has overseen global GxP compliance as a computer system quality SME for life cycle approach across multiple biologics departments in BMS. During this time, he has authored SOPs covering computer systems development life cycles from purchase to retirement, and is an expert in cGMP, GAMP, ISPE, JETT, and ICH. He has also previously co-authored two publications with Michael Rubacha regarding the use of Electronic Laboratory Notebooks. He can be contacted by email: anil.rattan@bms.com.

Bristol-Myers Squibb Co., 6000 N Thompson Rd, East Syracuse, New York 13057-4755, USA.

Michael Rubacha holds a BS in biology from the State University of New York at Albany. In 2006, he started with Bristol-Myers Squibb (BMS) as an assistant scientist in their Downstream Manufacturing Sciences and Technology Department. In 2008, Rubacha began working with Dr. Rattan in analytical systems management as a validation expert. During this time, Rubacha has validated close to 30 systems and performed risk assessments on hundreds of laboratory equipment. He is the current author of the system development life cycle SOP used within BMS' Biologics Development organization which details risk assessment, validation and qualification activities, relocations, preventive maintenance, calibrations, user administration, and periodic reviews. Rubacha is a current MBA student at Syracuse University with a projected graduation date in 2016.

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Current Events in Blend and Content Uniformity

by James S. Bergum, PhD, James K. Prescott, Ravindra W. Tejwani, Thomas P. Garcia, PhD, Jon Clark, and William Brown

This article presents a summary of the stratified sampling session held at the 2013 ISPE Annual Meeting.

In 1999, the Product Quality Research Institute (PQRI) established the Blend Uniformity Working Group. The purpose of this group was to make scientifically based recommendations on suitable procedures to ensure blend and content uniformity of a batch. The recommendation had to comply with 21 CFR 211.110 *Sampling and Testing of In-Process Materials and Drug Products*,[1] which require in-process testing for adequacy of mix. The recommendation provided an alternative approach to assess blend uniformity from that described in the former FDA guidance document, "Blend Uniformity" issued by the Office of Generic Drugs.[2] On 31 December 2002, PQRI submitted the group's final recommendation to the FDA,[3] which formed the basis for the FDA draft guidance for industry, *"Powder Blends and Finished Dosage Units — Stratified In-Process Dosage Unit Sampling and Assessment,"* issued October, 2003[4] hereafter referred to as the draft guidance document. Although the draft guidance document was never finalized, it was extensively used throughout the pharmaceutical industry. On 7 August 2013 the FDA withdrew the draft guidance document because it was no longer consistent with current Agency thinking.[5,6]

A group of individuals from the FDA, academia, and industry (sponsored by the International Society for Pharmaceutical Engineering (ISPE)) formed to discuss alternative approaches to assess Blend and Content Uniformity (BUCU) Group. This group sponsored a session at the ISPE Annual Meeting on 6 November 2013[7] to discuss the concerns that lead to the withdrawal of the draft guidance document. The session also included presentations for potential alternative approaches for the assessment of blend and content uniformity of solid dosage forms. The purpose of this article is to provide a summary of that session. Note that some presentations are not summarized here, in cases where permissions for publication were not granted.

Basis for the Withdrawal of the Draft Guidance Document

The primary reason for the withdrawal of the draft guidance document was that Sections V and VII no longer represent of the Agency's current thinking. Section V recommended taking at least three replicate samples from at least 10 locations within the blender. However, the guidance only required that one sample from each location be evaluated to assess blend uniformity as part of first stage testing. The FDA's current preference is to analyze all three replicates from each location.[6] The use of nested sampling plans and testing of replicate samples from each location allows the data to be subjected to Variance Component Analysis. This statistical technique divides the total variance into "between location" (the amount of variability across the sampling locations in a blender, or during a compression, encapsulation or filling process), and "within location" (the amount of variability between samples within a given sampling location). High between location variances often indicate poor mixing and non-uniformity within the blender, and also can imply non-uniformity or segregation during dosage form manufacture. High within location variances can be indicative of sampling bias (for blends) or incomplete mixing on a unit dose scale. Both variances are indicative of the quality of the batch.

The number of samples and the acceptance criteria contained in Section VII (Routine Manufacturing Batch Testing Methods) were based upon the limits published in the United States Pharmacopeia (USP) General Chapter

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<905> *Uniformity of Dosage Units*.[8] This was intentional to avoid any changes to the existing quality standard or an increase in the number of dosage units to be tested. The use of stratified sampling plans resulted in increased confidence for the uniformity of the batch, because sample locations target problematic areas prone to segregation or incomplete mixing. USP <905> *Uniformity of Dosage Forms* does not include a statistical sampling plan and is only intended to determine conformance of a defined sample. FDA's position is the results from USP <905> *Uniformity of Dosage Units* provide limited assurance that the batch meets specifications and statistical quality control criteria. [CGMP also requires sampling plans to be scientifically sound and representative of the entire batch (21 CFR 211.160(b)).] The FDA cited more statistically sound sampling plans and acceptance criteria that can be used to ensure the batch complies with current CGMPs, including 21 CFR 211.110, *Sampling and Testing of In-Process Materials and Drug Products*, 21 CFR 211.160 *General Requirements* [Subpart I, Laboratory Controls] and 21 CFR 211.165 *Testing and Release* [of the finished drug product] for Distribution.[1]

A science- and risk-based approach should be used to assess blend and content uniformity. Although powder thief sampling has known limitations, the FDA encourages industry to continue using the technique to assess blend uniformity (and identify errors when they exist), as well as more innovative approaches such as NIR[9] and Statistical Process Control (SPC) to assess blend uniformity. The technique(s) that companies choose to assess blend or content uniformity should be justified, including the number and size of samples, the position of probes, and the amount of sample measured.

The FDA recommends the use of stratified sampling plans when the batch contains locations that may have different results for a measured quality characteristic. The expectation is for the product quality to be consistent throughout the entire batch with no significant differences existing between locations. ASTM E2709[10] and ASTM E2810[11] can be referenced for establishing acceptance criteria for a stratified sampling plan.

Sampling Plans and Statistical Methods for Process Validation (Jim Bergum)

Sampling Plans

A sampling plan describes where (locations) and how the samples are taken from the blend or batch, and the number of samples (blend amount or dosage units) taken from each location. The most common plans are given below:

- **Simple Random Sampling:** each dosage unit has an equal probability of being chosen as a member of the units to be tested and are picked completely at random.
- **Stratified Sampling:** partitions the batch into "strata" (for example, first 1/3, middle 1/3, and final 1/3). The combination of all strata covers the entire batch. Then random sampling is performed within each stratum.
- **Systematic Sampling:** samples are taken at equal intervals throughout the batch. The first sample location is determined at random in the first interval then the remaining samples are taken at equal intervals from that point.

Typically for both simple random and stratified sampling, only one dosage unit is tested at each location which is called Sampling Plan 1. If greater than one dosage unit is taken at each location, the plan is referred to as Sampling Plan 2. Suppose 12 dosage units are taken from a batch and tested based on a systematic sampling plan using Sampling Plan 1. The variability in the results could be due to different locations or just the natural variability had all units been taken from the same location.

Figure 1 shows what the data would look like in the case where there is location to location variation (top half) and where there is no location to location variation (bottom half).

In the upper portion of the plot where there is location to location variation, the results at each location are similar, but there is variation between the locations. In the lower portion of the plot where there is no statistically discernible location to location variability, the within location variability is as variable as the variability between the locations.

ASTM E2709/E2810

The USP Uniformity of Dosage Units (UDU) given in General Chapter <905> Uniformity of Dosage Units of the USP UDU test is a market standard and is not intended for inspecting uniformity of finished product for lot/batch release or as a lot inspection procedure. Passing the UDU test once does not provide statistical assurance that a batch of drug product will meet specified statistical quality control criteria.

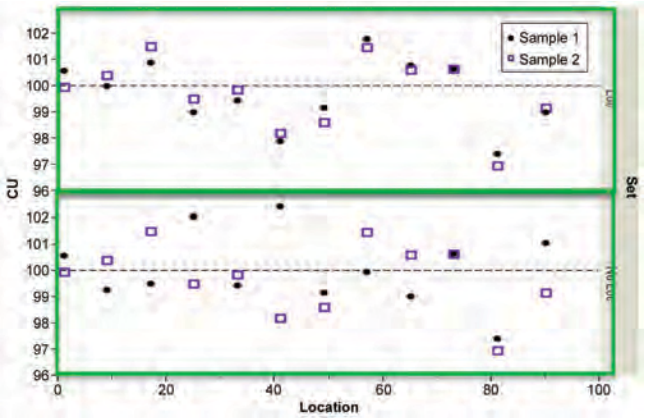

Figure 1. Batch data with and without location variability (CU vs. Location).

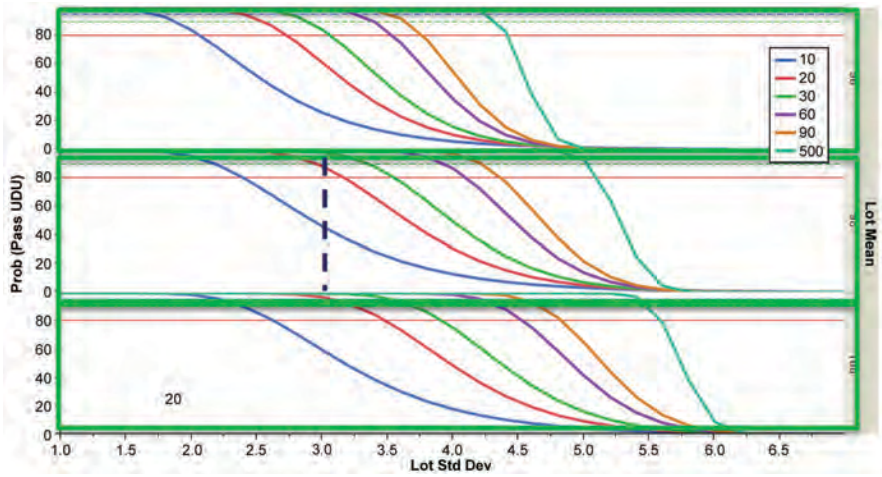

Figure 2. OC curves for Sampling Plan 1 (OC Curve = Prob (Passing Acceptance Limit Table for Specific Lot Mean and Standard Deviation)).

A methodology was developed by James Bergum[12] and updated by Bergum and Li[13] to provide this assurance that resulted in the following standards: ASTM E2709, "Standard Practice for Demonstrating Capability to Comply with an Acceptance Procedure" and E2810, "Standard Practice for Demonstrating Capability to Comply with the Test for Uniformity of Dosage Units." ASTM E2709 provides the general methodology and E2810 applies the methodology specifically to the UDU test. The goal is to develop limits based on the process validation sample results that would provide confidence that the testing standard samples would pass the testing standard. The method assumes that the content uniformity results can be approximated by a normal distribution. A summary of the methodology with examples is given in the Encyclopedia of Bio-Pharmaceutical Statistics.1[4]

As an example, suppose that a sample of 20 dosage units were taken from a batch using Sampling Plan 1 with a sample mean and standard deviation of 99% and 2.46% label claim, respectively. The ASTM E2810 acceptance limit table associated with this plan using a 95% confidence level and ensuring at least a 95% probability of passing the USP UDU test has an upper limit on the sample standard deviation for a sample mean of 99% of 3.52%. Therefore, this sample meets the criterion ensuring, with 95% confidence, that a sample taken for testing against the USP UDU test has at least a 95% chance of passing the UDU test.

Operating Characteristic (OC) curves show the probability of passing the acceptance limit table for various sample sizes. They are used to select a sample size. Figure 2 shows the OC curves based on 95% confidence intervals for batch means of 96, 98, and 100%LC and various sample sizes from 10 to 500 using Sampling Plan 1. Suppose based on lab data and current knowledge of the product that the expected 'true' batch mean would be above 98%LC and the standard deviation is less than 3%. The dashed vertical line is for a lot mean of 98% with a lot standard deviation of 3%. The dashed horizontal reference line is at 95% in the figure. So if we want a good chance of passing the acceptance limit table, a sample size of 30 would be reasonable.

Sampling Plan 2 is generally a systematic sample where more than one dosage unit is tested from each location. Suppose that a batch is sampled at 15 locations evenly distributed throughout the batch and four tablets are tested at each location.

The statistics required to use the acceptance limit table for Sampling Plan 2 are the overall mean, the within-location standard deviation and the standard deviation of the location means. Suppose these values are 98.93%, 1.07%, and 1.06%, respectively.

The acceptance limit table for Sampling Plan 2 contains limits for the overall mean for various combinations of the within-location and location mean standard deviation. If the acceptance limit table in this example was constructed using 90% Confidence with 95% coverage, the lower and upper limits on the overall mean are 89.1 to 110.9%LC. Since the overall mean in our sample is 98.93%LC, the sample passes the limits.

What Level of Variation is Acceptable (James Prescott)

As discussed in other presentations, different drug products could have different maximum and minimum potency values before the patient is affected by either an unsafe or ineffective dose. Note also that the patients themselves are variable one-to-another, in terms of body weight and how they respond to a given drug. If these limits were understood for a population of patients, one could then determine what the acceptable levels of uniformity could be for the product itself. This knowledge could be used to answer questions such as:

- What is the upper and lower acceptable limit for the potency of any single dosage unit a patient could receive (i.e., within the entire population/batch that is released)? Note this is different than limits on values for a single dose that is *tested* from a smaller subset of a population. For example, a batch with a mean of 100%, an RSD of 6.0% and a normal distribution would theoretically have 31 of 1,000,000 tablets outside of 75 to 125%. In this case, 31 consumers may receive tablets that could be unsafe or ineffective. There would be a low probability of directly measuring these specific tablets via most sampling plans, but these nonetheless would be released as part of the

batch (if a 6% RSD were acceptable).
- Does the variation matter solely from tablet-to-tablet or could it matter bottle-to-bottle (of tablets)? For example, a single tablet being low might not matter if the overall course of treatment is at the target value. On the other hand, if the bottle overall is sub-potent, this might have more of an effect than if a single dosage unit is low. In some manufacturing processes, the dosage units are packaged in a sequence closely aligned with when they were created. Other processes (such as film coating an entire batch) randomize the dosage units such that there is no connection between packaging and dosage unit creation, in terms of the sequence. This could have an effect on the sampling plan and acceptance criteria.

If the acceptable level of uniformity is understood for the patient, in terms of either single dosage limits or overall treatment limits, this could be translated to specific sampling plans designed to detect these limits.

What Could Effect Uniformity

Sampling and testing is done to challenge the assumption that the product is sufficiently uniform. If no special causes that can create non-uniformities are present, and all variation throughout the entire population is by random variation, one would expect a normal distribution. In this case, the population's uniformity could be reasonably estimated with a limited number of samples to determine, within a range of certainty, an estimate of what the population mean and standard deviation would be. The sole question would then be what an acceptable range would be for a population mean and population standard deviation.

However, the assumption that no special causes are present is not valid when non-uniformities arise. Reasons for non-uniformity include: poor blending, segregation from the blender to the creation of a dose, poor particle dispersion (e.g., agglomerates), losses of components or dispensing errors, and product weight variations. Non-uniformities also can *seem* to be present due to sampling problems (e.g., thief sampling errors) or due to analytical errors. Each of these root causes can result in different forms of variability or signals. These signals, if correctly captured and interpreted, can point back to the likely root causes.[15]

Since these signals are not occurring randomly, but as a function of when and where the problems arise in the manufacturing process, sampling must include samples produced during these points. Therefore, in defining an appropriate sampling plan, some fundamental knowledge of what to look for, and where/when to look for it, is required; otherwise, a very large number of samples may be needed to cover all the bases. For example, it is generally recognized that segregation can lead to non-uniformities particularly at the very beginning or very end of discharge of a bin. Focusing sample collection in these areas can be a better use of resources to challenge whether segregation occurred, rather than simple random sampling. This was the rationale for targeting "significant events" in the draft guidance document.[4]

Separating out within-location vs. between-location variations is one critical aspect in understanding uniformity, as these variations are attributed to different root causes. For example, within-location variations are usually attributable to poor dispersion of the active drug due to poor micro blending or agglomeration, sampling/analytical errors, or just random noise in the process. Between-location variations are usually attributable to poor macro blending or segregation. Having a single sample from a given location might show an unacceptable result, but does not allow for distinction of the possible source(s) of the problem. Further, if there is high within-location variation, there is a risk that a single sample from a given location might be non-representative of the location as a whole, e.g., the location is superpotent overall, but the one sample analyzed is close to target. Note that for a location to provide relevance in this sort of analysis, the samples that represent the location must have been collected from essentially the same time point or position. Factors that could negatively influence this approach include sub-sampling from a larger sample, sampling error (in the case of thief samples), and physical differences during the dose creation (multiple stations or lanes on the forming machine).

Not all non-uniformities are equal. A batch which has normally-distributed data, shows mostly within-location variation, with all locations being statistically identical, would suggest a process where random variation alone is occurring, without any special or assignable root causes. This gives a higher degree of assurance that all dosage units would have the same random variation, and thereby less concern that there are undetected dosage units that would be worse than that estimated by statistical inference. On the other hand, data which shows tails, non-normality, and/or locations that are different than others (high between-location variations), imply that a special cause may be occurring, which might lead to intervals during manufacturing which are even worse than those that were sampled.

A question that must be addressed with any sampling plan and acceptance criteria is whether any or all specific problems (blend non-uniformities, segregation, agglomeration) must be targeted with specific, customized sampling plans, or whether the approach can allow these potential problems to be uncovered by other means.

Holistic Considerations

Understanding the uniformity of a particular batch is never done in the vacuum of just looking at uniformity of the dosage units. There is prior knowledge of many factors that could give rise to or prevent uniformity issues, such as the

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drug loading, whether the blend is a dry blend (e.g., direct compression) or granulated (e.g., wet granulated, roller compacted, spray dried), the particle size and shape of the components (which may give some insight on dispersability, agglomeration, and segregation potential), cohesiveness/stickiness of the blend and/or its components, the scale of handling (e.g., development vs. manufacturing) and the process/equipment being employed (e.g., in-bin blending, scoop vs. automated feed of the press, isolation features for press feeding). Long before the first sample is pulled, one can already have one or more hypotheses that should be tested to demonstrate that sufficient uniformity is likely to be achieved and maintained.

Once multiple batches have been made, comparison between the current batch under consideration and all prior batches also could come into play. A change in behavior can be as telling as the actual values themselves. For example, a process which has a long history of <2% RSD could be looked into when a 5% RSD is noted, even if 5% is otherwise acceptable. Another example is if all batches had mean values between 99 and 101%, a result of 97% could be a warning indicator.

Comparison of Blend Data to Product Data

Product (dosage unit) uniformity is the sole area of concern for the patient, as they are only consuming dosage units and not samples from the blender. However, blend uniformity data can provide additional insight to batch uniformity, provided that one can rely on the samples collected from the blender as being unbiased/without error, which is often not the case. "Adequacy of mixing" is also required per CGMPs although demonstration of an adequate mix can be achieved without using samples from the blender itself.

If one has reasonable assurance that blend sampling errors are not occurring, comparing blend uniformity data to product uniformity data can provide further insight as to possible manufacturing issues. For example:

- A decrease in overall potency from the blender to the dosage units could be an indication of losses of active during manufacturing.
- An increase in between-location variations could be an indication of segregation during transfer.

Blend data and content uniformity data should be compared, but they may not be correlated. If both have variations solely due to random noise, they will not be correlated. If correlated (high BU RSD translates consistently to high dosage unit RSD), special causes for variations are present, such as incomplete mixing of certain batches or variations in raw materials that create non-uniformities that translate from blending through to the dosage units.

Some Common, Specific Questions that are not Well-Addressed Currently

Common sampling strategies and acceptance criteria have not addressed the following questions, which seem to arise regularly:

- Does one need to consider the uniformity/quality of the blend at the very beginning or very end of compression, if these portions of the batch are waste? If not, could the tails be extended intentionally, e.g., longer start-up period, earlier shut-down, so as to avoid having a uniformity problem?
- Should normality of the data be considered, and if so, what deviation from normality should cause concern? What test(s) should be used for normality? Should normality tests be restricted to each single batch or the process as a whole?
- If a process has consistently shown excellent uniformity (e.g. >10,000 dosage units tested over many years, with an average batch RSD of 2.3%, normally distributed), and one day a single dosage result of 136% is found without any assignable cause after extensive investigations (no manufacturing or laboratory errors found, no deviations from normal), should this *require* any process improvements or new controls, or is this just the tail of normal, random variations that were occurring all along? Does this result call into question the process or product?

Relationship of Blend Uniformity to the Finished Drug Product Uniformity and Performance Variability (Ravi Tejwani)

Typical Sources of Variation

In a given powder blending based manufacturing process, several possible sources of variation exist. Broad classes of these include those arising from the material properties, manufacturing process, and from the measurement systems. While not always feasible, material properties can be mitigated to some extent to minimize the dosage form variability. The constraints resulting from material properties (e.g., particle size, choice of process, type of blend formed by a given material), unless mitigated, tend to be limiting in the sense that they cannot be overcome by making changes to the manufacturing process. The manufacturing process related variations could arise from either the process design (e.g., insufficiency of blending time, too fast a filling process to allow sufficient time for filling or a dispensing system) or the errors in the execution of an established process that is known to produce uniform product (also referred to as control system variability, e.g., RPM calibration of the blending equipment or weight control on a dispensing system such as a dosator or a fill cam). Typical product development activity should include a systematic study of all applicable sources of variation and ensure that their contributions

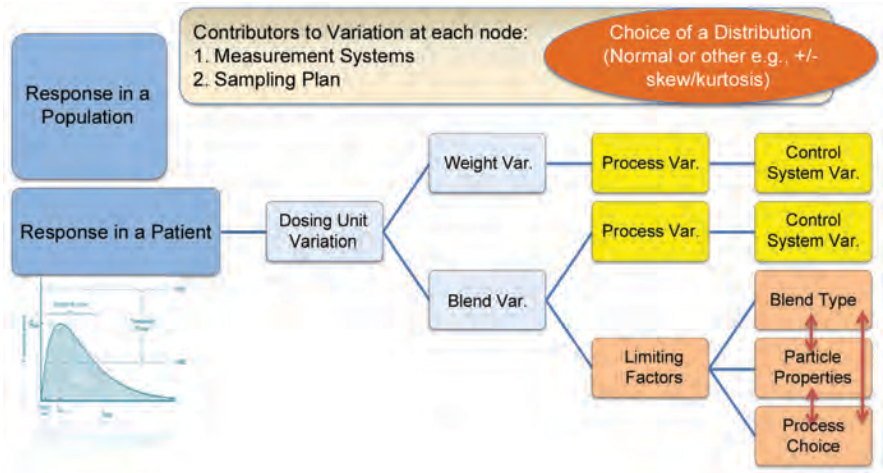

Figure 3. Relationship among the typical sources of variation in a drug product.

remain under control. The relationship among the typical sources of variation is shown in Figure 3. During the product development as well as during routine manufacture an additional source of variability is often realized, and that is the variability of the measurement system (errors of sampling as well as the error of measurement). Most frequently cited examples of sampling are the design of thief during powder sampling, and inadequate protocol employed in sampling of the finished dosage units. The error of measurement is usually easily accessible through the validation of the analytical methods.

Considerations for the Limiting Factors

Factors such as particle size of the active ingredient and the type of blend are usually decided earlier in product development and determine the best possible dosing unit precision that a manufacturing process can deliver. For example, uniformity of a random blend increases to a limiting value in a blending operation; however, it never approaches as high as that of a structured blend. This is one of the reasons for adding a granulation unit operation in a manufacturing process. Reader is referred to literature for more detailed discussion on the blend types[16] and the effect of particle size of active[17] on the uniformity of blends and dosing units.

Accountability for Multiple Sources of Variation – It is all about Bookkeeping

Often reported thief related errors (one of the two components of the blend measurement system) sometimes make blend variability appear higher than it is, leading to an abandonment of the BU approach altogether because the dosing unit variability is shown to be much lower than that of the blend. If a reasonable effort is made to decrease (or accounted for properly) the sources of error in the measurement systems, this anomaly usually disappears. After all, the dosing units are prepared from the blend by some sampling method (a dosator, a screw feeder, or a tablet press die with a fill cam). In a possible scenario of lack of any feasible blend analysis method, at the very least, a good correlation between the dosing unit weights (W) and the potency (D) can be demonstrated as an indirect evidence of blend uniformity. In the following equation, the residual term in the regression between D and W should contain the information about the blend uniformity:

$$D = WB \qquad \text{Equation 1}$$

Where D = dosing unit potency, W = weight of the dosing unit, and B = concentration of the active in the batch of blend that was used for weighing the dosing units. Absence of such a correlation may signal the need for further investigation. Finally, the quantitative amount of the "unaccounted variance" allowed for a given product depends on the specific risk benefit profile of the product (discussed further under the Biorelevance topic below).

It also should be noted that the uncertainty of the estimates of variability depends on sampling related factors: 1) the aliquot size (or dosing unit size) and 2) the number of aliquots (in case of blends) or the number of dosing units. It should be noted that the most relevant size of powder blend aliquots is the same as the target weight of the blend in the

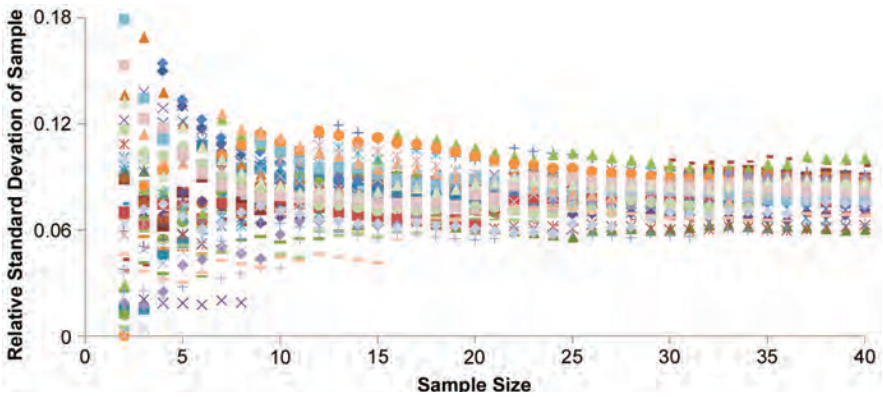

Figure 4. Relative Standard Deviation as a Function of Sample Size. The Samples are drawn randomly from a Batch of 100,000 units simulated with an underlying mean of 1 and Relative Standard Deviation of 0.08. Symbols indicate different samples drawn from the same batch.

dosing unit. Any larger aliquot size would lead to a more liberal estimate and a smaller aliquot size would lead to a more conservative estimate.

During the product development phase, only a reasonable estimate of the variability is desired (e.g., to guide next steps in product or process design) as opposed to adjudicating the release of a batch. Determining the number of aliquots or dosing units needed to estimate variability in absence of an acceptance criterion can be difficult. In this situation, a point of diminishing returns exists near 30 to 40 units as shown in Figure 4. Data interpretation (as to the true variance of the batch) should take into consideration that significant uncertainty still remains in the estimate of the variability. For example, approximately one third of samples (at n = 10) will show a RSD less than 0.06 despite the batch RSD at 0.08 (i.e. 1/3 odds of erroneous acceptance).

The exercise in Figure 4 was repeated for various batches with differing RSD values. This type of simulations suggest that a sampling spread of approximately 50% to 150% exists around the batch RSD values at a sample size of 10 (target RSD of 8 has a spread from approximately 4 to 12). This spread remains the same irrespective of the batch size simulated or its RSD. Based on this, one would not expect multiple samples of 10 dosing units each (or powder aliquots each) conform with each other, let alone the blend samples relating to the dosing units.

The manufacturing process related sources of variation (e.g., number of blender revolution) can only be studied after assuring that the measurement system (sampling and analytical) variability is lower than the former.

Biorelevance of the Uniformity Specification: A Separate Specification for Each Product

For a given drug, the favorable and unfavorable responses are considered to be related to the quantity of the active drug administered.[18] Both types of responses are generally correlated to the concentration in the central tissues such as blood or plasma. Since most dosing regimens involve some type of periodicity in multiple dosing, it is reasonable to conclude that the preceding statements relate to the steady state concentrations as opposed to the concentrations obtained from single doses. Further, if the dose response (favorable or unfavorable effect) of a given drug is driven by the area under the concentration time profile (AUC), the AUC obtained at the steady state of multiple dosing is relevant. Following is a set of simulation studies undertaken[19] to evaluate the effect of variation in the dosing unit content on the *in vivo* concentrations.

In each of the simulations below, the pharmacokinetic parameters for each drug candidate, (amoxicillin[20] and levothyroxine[21]) were obtained from the respective published studies in the literature. Relative standard deviation values of 6.5%, 13%, and 20% were simulated for 500 mg amoxicillin, and values of 1%, 2%, and 6.5% were simulated for 150-mcg levothyroxine.

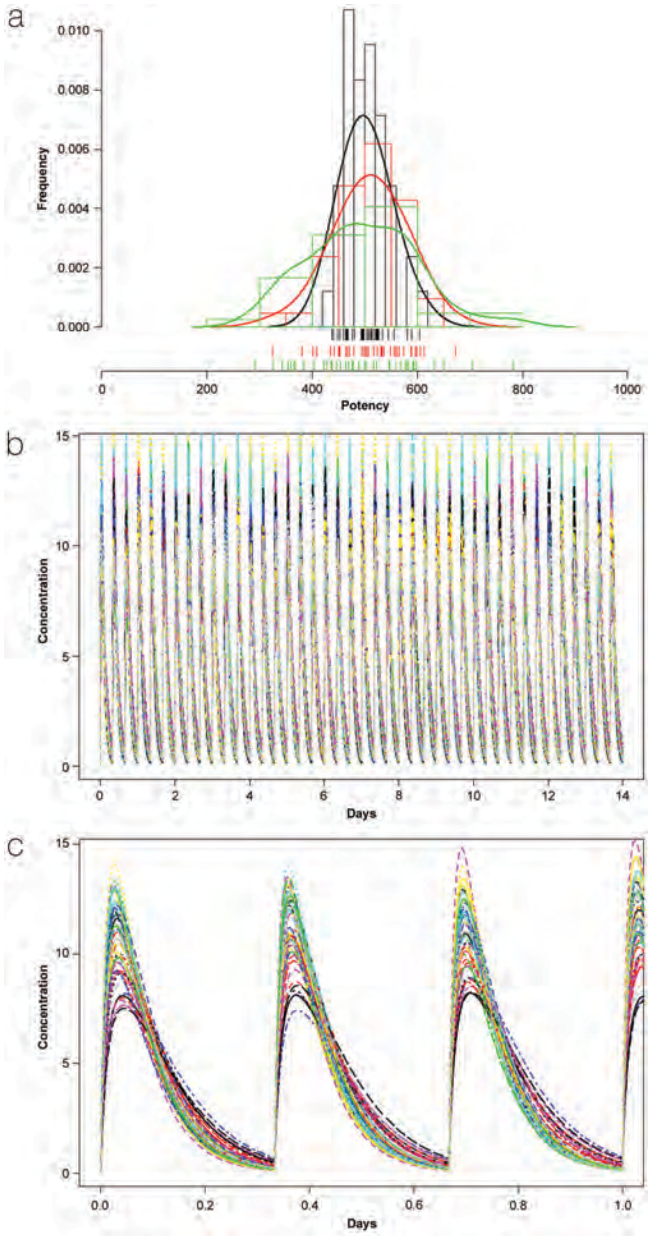

Figure 5. Simulated Potency Distribution and PK profiles for Amoxicillin 500 mg. Panel A: Potency distributions of the tablets used as input for pharmacokinetic simulation, Panel B: Plasma concentration vs. time profile after multiple dosing for 13% RSD tablets in a clinical trial with 48 subjects, Panel C: Magnification of Panel B. Color codes for Panel A: Black = 6.5% RSD, Green = 13% RSD, Red = 20% RSD. Each color in Panel B and C represents a simulated subject.

It is known that multiple dosing of an active leads to a "loading" phase and a "maintenance" phase to the dosing regimen. The two phases are clearly apparent in cases where the steady state C_{max} is a multiple of the C_{max} levels observed

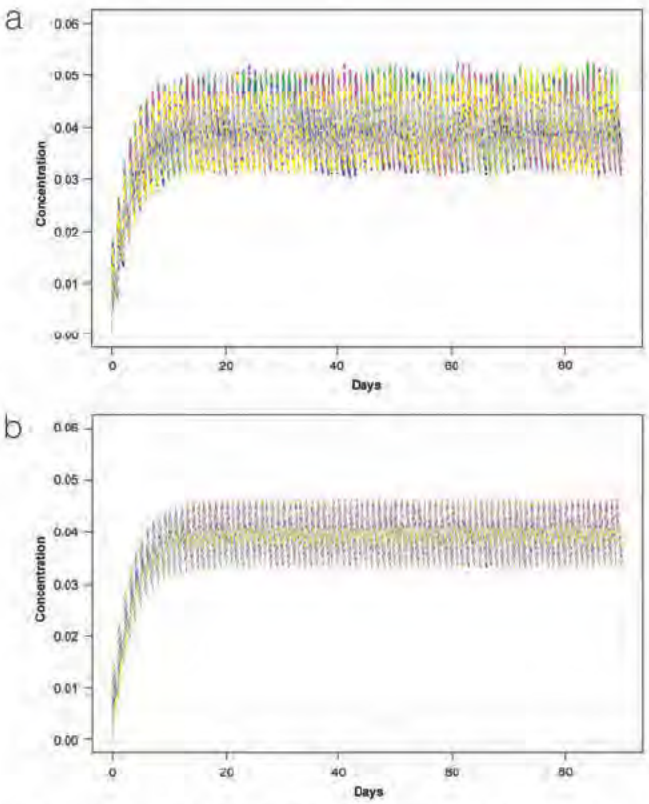

Figure 6. Simulated PK profiles for levothyroxine, 150 mcg. Panel A: Plasma concentration vs. time profile after multiple dosing for 6.5% RSD tablets in a clinical trial with 48 subjects Panel B: Pharmacokinetic simulation of 1% RSD tablets in a clinical trial with 48 subjects, each color in Panel A and B represents a simulated subject.

after a single dose (e.g., levothyroxine, Figure 6); and not so apparent in cases where the steady state C_{max} is close to the C_{max} observed after a single dose (e.g., amoxicillin, Figure 5).

In the case of amoxicillin, where usually time spent above a certain minimum concentration relates to the biological efficacy; variations of as high as 13% RSD in the tablet potencies lead to relatively small perturbations in the time spent above a given concentration in the simulations. Further, the simulations show that the C_{max} may change from dosing unit to dosing unit (a parameter correlated to the potency of each unit). Since typical safety margins are larger than a few multiples (assumed), the variation in C_{max} observed for amoxicillin is not likely to traverse the thresholds.

In case of levothyroxine, the pharmacologic activity depends on the maintenance of the levels of the hormone within a narrow concentration window. The width of the C_{max} to C_{min} window at the steady state becomes a concern given the fact that a dose level of 137 mcg is considered clinically different from 150 mcg. The simulations show that the dosing unit variations of 6.5% would exceed the lower threshold, and a 1% or 2% RSD standard may be more appropriate.

The limits specified in USP <905> allow for approximately 6.5% RSD for dosing units, irrespective of the specific drug properties. The simulations above demonstrate that significantly different limits could be applicable for each drug depending on its pharmacologic profile. Sufficient information regarding the dose response and manufacturability of a given drug candidate may be available to allow for establishing such a requirement for dosing unit precision.

Going Forward

The BUCU Group intends to publish a paper (Spring 2014) which defines alternate approaches for the assessment of blend and content uniformity. The intent is to identify a number of techniques to assess blend and content uniformity, rather than rely on a single approach.

In addition, discussions have occurred within the group since the November session regarding the potential impact that the group's output will have on USP General Chapter <905> Uniformity of Dosage Units. USP recognizes that the USP <905> is specific to compliance testing of finished drug product and is not intended to evaluate the acceptability of whole batches of units that were not subjected to the test. The emergence of consensus standards such as those cited in this text provides an opportunity to strengthen the USP standard by inclusion of these concepts. This could provide a

readily available source for these standards and unambiguously apply them to USP articles. In addition, the process of developing a USP chapter will include oversight by the USP Council of Experts, as well as providing an additional round of public comment for those who may not be focused on other sources of product standards. The pharmaceutical community could engage in a public discussion to determine how well a USP chapter such as this would be accepted. That said, the withdrawal of the draft guidance document serves this purpose in that it is the removal of a batch release recommendation, a portion of which was inappropriately based on the compliance testing chapter USP <905>. The full impact of this new approach can be explored in additional publications that can focus on the ability to advertise product quality through compliance with a public quality standard.

The group's recommendations and the impact they will have on USP <905> will be discussed at the 3rd Annual ISPE – FDA GMP Conference (Baltimore, Maryland; 2-5 June 2014).

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Acknowledgements

Karthik Iyer, Alex Viehmann, and Huiquan Wu.

About the Authors

James S. Bergum, PhD received his PhD in statistics from Montana State University (1981). Bergum worked in nonclinical biostatistics for Wyeth from 1981 to 1988 and Bristol Myers Squibb from 1981 to 2012. His primary job responsibility was to provide statistical support to research and development, including design and analyses of experiments, analytical assay development and method validation, process validation, stability, drug safety evaluation, and teaching short courses to scientists. He developed a statistical method that resulted in two ASTM methods (ASTM E2709 referenced in the FDA guidance for Process Validation and E2810) that can be used to evaluate development, process validation, or release data. After retiring in 2012, Bergum started BergumSTATS, a statistical consulting company specializing in statistics related to Chemistry, Manufacturing, and Control (CMC) issues. His current interests are statistical methodologies that can be applied to product development, process validation, and manufacturing.

James K. Prescott is a Senior Consultant and Director at Jenike & Johanson, Inc. in Tyngsboro, Massachusetts. Jenike & Johanson is a specialized engineering firm focusing on providing reliable bulk solids flow while achieving product quality requirements. Prescott's focus has been primarily on pharmaceutical applications, such as solving and preventing content uniformity problems, maintaining reliable feed, reducing product weight variations, developing specialized feeders for low feed rate/high accuracy applications, and standardizing handling equipment. He holds patents on equipment related to segregation testing and equipment to control segregation. He received his BS in aeronautical engineering from Rensselaer Polytechnic Institute, and his ME in mechanical engineering from Worcester Polytechnic Institute. Prescott is a member of the USP committee working on standards for shear cell testing, and was a member of the PQRI Blend Uniformity Working Group.

Ravindra W. Tejwani was trained as a pharmacist and has worked in the pharmaceutical industry for more than two decades. He has earned his MS in pharmaceutical sciences from the University of Mississippi and his PhD in pharmaceutical sciences from the University of Kentucky. He has been author or co-author of many publications, conference symposia, and patents. Tejwani maintains interest in computational modeling and simulation of the phenomena in pharmaceutical sciences. In this area, his recent works include molecular dynamics simulations of the lipid bilayer membranes, prediction of content uniformity, and biorelevance of content uniformity. In his role at BMS since 1997, he has been involved in several positions of increasing responsibility and has led development, scale up and technology transfer, and commercialization of new drug products.

Thomas P. Garcia, PhD is a Research Fellow in Global CMC, Pfizer Inc., Groton, Connecticut. He received a BS in pharmacy from Albany College of Pharmacy in 1983, and a PhD in industrial and physical pharmacy from Purdue University in 1989. Garcia spent 14 years in the pharmaceutical industry in process development and technology transfer, where his primary interests were powder mixing, blend sampling, and the use of statistical techniques to optimization and assess process capability and robustness. He joined GCMC in 2003 has been active in defining regulatory strategies related to Quality by Design (QbD) dossiers. Garcia is an Adjunct Associate Professor in the Department of Pharmaceutical Sciences at Albany College of Pharmacy and Health Sciences, and held the same position at Campbell University from 1996 to 2000. He was a member of the SUPAC IR Industry Training Committee, served as Chair of the PQRI Blend Uniformity Working Group, and was a member of the ISPE PQLI Control Strategy Task Team.

Jon Clark brings many years of experience in the global pharmaceutical industry and more than 20 years of experience with the US Food and Drug Administration (FDA). For the last 10 years at FDA, Clark has held the title of Associate Director for Program Policy, Office of Pharmaceutical Science, in FDA's Center for Drug Evaluation and Research. As Vice President, Clark will lead the development of new monographs in both the United States Pharmacopeia-National Formulary (USP-NF) and the USP Medicines Compendium (MC), focusing on the possibility of comprehensive monographs that are potentially suitable for all three compendia. Clark will work closely with Todd Cecil, PhD,Vice President of Chemical Medicines – Monograph Modernization to advance a full cohort of monographs. He holds an MS in chemistry from Rutgers University and a BS in chemistry from University of Michigan Ann Arbor.

Will Brown is Senior Scientific Liaison to the USP Pharmaceutical Dosage Forms Expert Committee. He has been involved with the harmonization of the USP general chapter <905> Uniformity of Dosage Units over the last 10 years.

BRAZIL. More than 500,000 new cases of cancer arise every year, and the disease is currently the second most common cause of death in the country.


SOUTH KOREA. In early 2013, Samsung Biologics started operation of their large-scale multiproduct MAb facility which produces treatments for, among other things, various types of cancer.
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Project Execution Planning: The Key to Successful Pharmaceutical Project Delivery

by Robert Garner

This article presents the importance of a Project Execution Plan (PEP) for a pharmaceutical facilities project, outlines the fundamental aspects of a PEP, and details what should be included in each section.

Every pharmaceutical project is unique and each project requires a detailed Project Execution Plan (PEP). The PEP is not a "one size fits all" document. It must be specifically tailored to meet the size and specific phases of an individual project.

While attributes that are common to all projects include safety, quality, cost, and schedule, each project combines differences in scope, scale, complexity, resources, and many other factors to achieve its goals and objectives. During the project development and delivery process, the concept and Basis of Design (BOD) phases of work are important alignment phases of project execution which help to address these attributes as well as many addressed within the PEP. The PEP communicates and documents the project "map" and the overall strategic approach for the execution of the entire project for all stakeholders. It also sets the tone for demonstrating effective leadership, project organization, progress measurement, and teamwork. A good PEP provides guidance over every applicable element of a project. Such attention to detail is particularly important for the pharmaceutical industry, which faces regulation from the U.S. Food and Drug Administration (FDA) in the form of current Good Manufacturing Practices (cGMP) regulations. A PEP is the product of good project planning and incorporates several sub-plans, such as a project procurement (or supply management) plan, project risk identification and mitigation plan, project staffing plan, construction execution plan, cost/budget management plan, project controls plan, project quality plan, and overall team alignment.

The PEP is typically completed during the early (concept, BOD, or preconstruction) phase of the project. Preconstruction is critical for the successful delivery of capital projects.

Figure 1. Key Project Execution Plan (PEP) elements.

These early phases of a project provide owners with a formal approach for developing and executing capital projects. In addition, these early phases help define the project scope, schedule and cost as early as possible to enable the most efficient use of resources and money, while reducing risks as seen in Figure 1. In order to achieve the necessary level of accuracy, project execution planning must be performed in conjunction with the project's capital planning. Only by tying budget items, line-by-line, to construction tasks can a precise PEP be established.

A PEP should be tailored to meet the size, scope, and execution approach agreed upon for a project. For instance, a PEP that is used for a $200 million Engineering, Procurement and Construction Management (EPCM) plan should be more detailed and extensive than one for a $1 million design-only project. The key components of the plan should be the same, but the level of detail is different. Every project should have some form of PEP or alignment document that encompasses the scope and organization of the project and sets the cadence at project kickoff.

While the PEP provides guidance for the execution of the project, it usually starts with a mission statement or overall goal of the project based upon the owner's requirements, such as scope, technology, business drivers, owner involvement, schedule, operations, project size, regulatory environment, permitting, commissioning, licensing involvement, and expectations for ROI. An example of a simple mission statement might be to deliver the new ABC manufacturing facility in a phased approach that is aligned with the Company XYZ manufacturing strategy and supports the business objectives of its supply chain. Key items to accomplish with this mission include:

- To meet Phase 1 production dates and requirements in 1Q2014 and Phase 2 in 3Q2015
- To provide the new facility and support facilities in a manner that support the production goals stated above
- To create a safe, productive, collaborative and highly motivated work culture that supports the achievement of these goals

The following discussion provides some key elements that should be covered in a PEP - *Figure 2.*

Project Scope

It is important to outline the scope of the project, as it forms the basis for the effort-hours and overall schedule required to complete the project from a design, procurement or con-

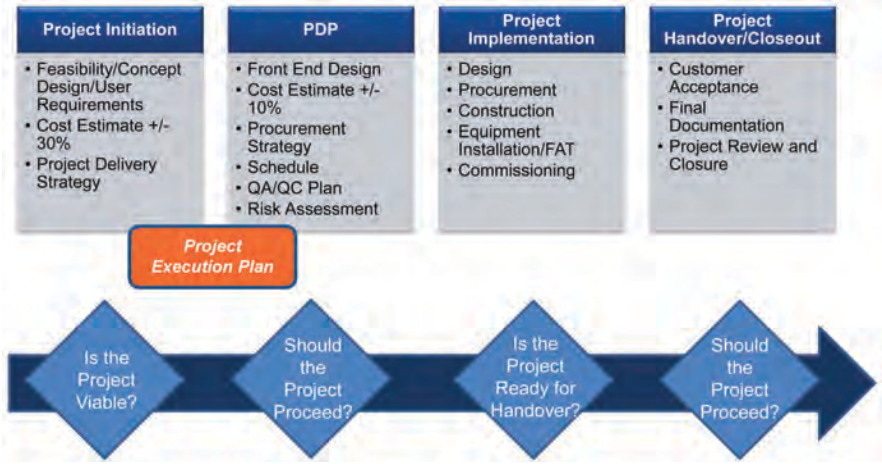

Figure 2. Key project execution activies – based on *ISPE's Good Practice Guide: Project Management for the Pharmaceutical Industry* project type matrix.

struction perspective. It also forms the basis for the project management constraint triangle: scope, cost, and schedule. Obviously, the larger the project (defined in scope), the greater the design, construction, and procurement effort it will take to complete. The scope of work is a critical element for cost and schedule management of the project, and is the foundation of the project. Essentially, the PEP defines the "what" and "where" work will be derived.

Project Organizational Chart

Who is in charge? Who has the authority to allocate costs and make changes? What is the project reporting structure? How does the team fit together? This should be made clear up front and updated as required.

Contracting Strategy and Project Delivery Model

Is the project EPCM, design-bid-build or other? The PEP should reflect the planning of the project and state the delivery model being utilized. Many specific elements of the PEP are addressed regardless of the contracting strategy, but clearly the PEP will address these requirements from a roles and responsibilities perspective differently depending on the delivery model chosen. The key is to put these thoughts into the PEP and clearly communicate these intentions for the entire team early.

The project delivery decision should be based on a number of factors including budget, schedule, cash flow, project complexity, risk mitigation, project team composition and project goals. Essentially, a project delivery method is a configuration of roles, relationships, responsibilities, and sequences on a project.

A brief overview of some of the typical project delivery methods for pharmaceutical projects can be seen in Figure 3.

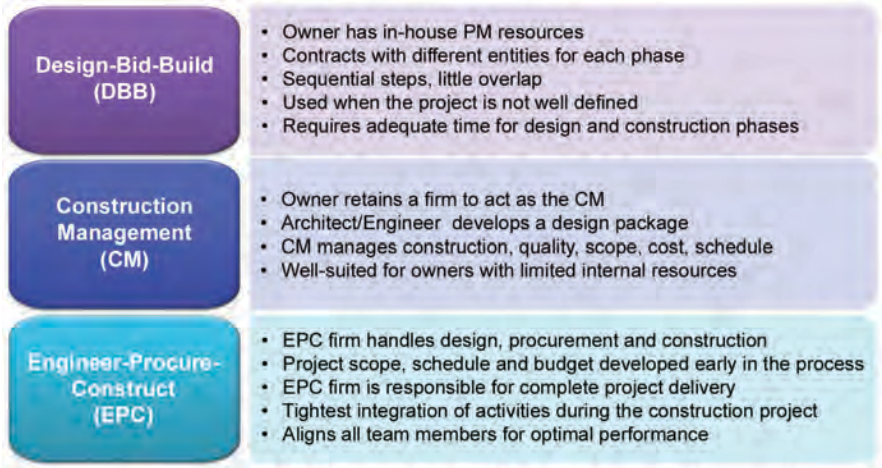

Figure 3. Typical project delivery methods used for pharmaceutical projects.

Design-Bid-Build (DBB)

DBB is a common project delivery method in the pharmaceutical industry. Owners with sufficient in-house staff contract with different entities for each phase of design and construction, and take on the responsibility of orchestrating the various team members. Each step in the execution process follows the other with minimal overlap. Under this approach, the owner functions as the overall project manager and hires external engineers, consultants, and contractors.

DBB is typically used when the project is not well-defined and there is adequate time for the design and construction phases. These projects are often competitively bid and priced as a lump sum. The competitive nature of the bidding process usually results in a competitive cost for the owner, but the quality of the subcontractors is left to the general contractor.

Under this method, all construction and performance risks are assumed by the GC. Change orders and schedule delays can occur if the owner's intent for the scope of work is not well-defined by the architect to the contractor.

Construction Management (CM)

Under the CM method, the owner retains a firm to act as its construction management representative. There are a number

of variations on this model. An architect is retained to develop a design package. The CM is retained for a fee and is responsible for managing construction while meeting goals in terms of quality, scope, cost, and schedule.

The CM representative is also responsible for estimate development, construction, subcontracts, scheduling, reporting, quality control, and cost controls. Then architects, engineers, and consultants are retained to develop a program. Multiple construction packages are developed, and bids are solicited from various trades. Under the CM method, design and construction activities overlap.

This model is well-suited for owners that lack in-house design and construction expertise or capacity. It ensures consistent oversight and careful monitoring of costs and schedule. However, this method can result in additional upfront costs and create communication challenges among the team.

Engineer-Procure-Construct (EPC)

EPC is emerging as a preferred choice of project delivery for pharmaceutical projects. Under this model, the EPC firm handles design, procurement of all equipment and construction materials, and construction services for complete delivery of the project, usually at a lump sum price. The EPC process starts with a preconstruction effort that involves some preliminary planning and engineering to define scope, schedule, and costs of the project. The EPC firm has complete responsibility for the project from start to finish.

The project schedule and project budget are known at the start. All scope, cost and schedule risks are passed to the EPC contractor. EPC project delivery offers the tightest integration of activities during the construction process through a structured and disciplined approach. In addition, communication among the design, procurement, and construction teams begins immediately.

The EPC model helps align team members for optimal project performance. EPC delivery is typically used for process or equipment-driven projects. This model reduces risks for the owner, delivers predictable results, and maximizes the effectiveness of capital planning.

The project delivery method will have an impact on the PEP. Clearly, the level of planning will be substantially different for a single source EPCM project than for a design-only PEP, so this should be covered first.

Project Contractual Arrangement

There are many collaborative methods used to properly incentivize a project. The project contractual plan should determine how the scope of work will be performed by contactors to meet the project objectives. The contract plan should address roles and responsibilities, project scope of work, contracting methods, and project milestones.

Different contractual terms have different impacts on project stakeholders. For example, is the project cost plus fee, guaranteed maximum, or lump sum? These approaches are typically negotiated. The key point is to maintain as much "skin in the game" for all parties as possible. This will ensure that the project gets proper focus from all parties until completion. Another area of focus should be the alignment of the owner and equipment suppliers. All project stakeholders should understand their role and work collaboratively from the outset; this information should be within the PEP.

Properly covering scope in a PEP helps each team member to properly allocate time and effort. Generally speaking, everyone involved wants to do a good job on a project and have a successful outcome. It is in the execution of the work and in the communication of what needs to be done, when it needs to be done, and in the prioritization and planning of the workflow that problems occur. By properly communicating the project scope, one can be sure that the entire team has the best chance for success from the start; they can sit down and plan exactly what needs to be completed during each phase of the project.

Finally, by effectively documenting the project scope from the outset, a record is created that forms the basis of change management if indeed the scope changes (either increases or decreases) as the project evolves. Change occurs in every project and alterations in a project's scope must be properly managed by the project manager and accounted for in both schedule and budget. The PEP is a great place to baseline these elements.

Project Risk Identification and Mitigation

What special risks does the project have that need to be monitored and mitigated against? It is critical to beware of potential risks and to develop mitigation strategies to ensure the cost and schedule are met. Common examples of project risk include: use of new or unproven technology, impact to existing facilities or operations, project cost, project schedule, validation of new technology or products, compliance, etc. Project risk should be defined and managed.

In a generic sense, risk can be defined as: the probability of an uncertain (unwanted) event X (times) the severity of this event.

Within a PEP, the project manager needs to identify and communicate risk in terms of both probability and severity and then needs to plan risk controls to mitigate each. Risk controls can include people, funds, time and other resources. Mitigation involves reducing the probability or severity of an event. Proper mitigation planning also can involve the utilization of a "backup" plan that is used in the event that a project risk becomes reality. The PEP should introduce a project management action log, and this log should be reviewed and updated monthly. It should visit each potential project risk and assign a status to the probability of this risk

in realtime as the project goes forward. This status should be communicated to others who will be impacted or who should be informed. For more specific guidance on managing project risk on pharmaceutical projects, the reader should consult the *ISPE Good Practice Guide: Project Management for Pharmaceutical Industry*, Chapter 3, pages 61 to 84, as this provides a very good overview of risk management in the pharmaceutical industry.

> *"The PEP should include discussion of how costs and schedule will be managed during the design, procurement and construction phases of the project.*

Cost and Schedule Management

The PEP should include discussion of how costs and schedule will be managed during the design, procurement and construction phases of the project. The cost management plan should determine how costs will be estimated, reported, controlled and managed. On any project, costs are driven by a combination of scope of work, resources and productivity. This will serve as a guide for the project, starting with the original project schedule and budget through completion. This should include cost development, cash flow, milestones and other factors related to the costs and schedule of the project. Schedule management discussions should focus on how the schedule will be prepared and tracked and how milestones will be set and measured.

Procurement Strategy

Two distinct elements of this strategy are discussed below:

Package Definition – for each piece of equipment, material or construction trade, the team must develop a list of non-overlapping documents (packages) that form the basis for each purchase. This typically involves extensive planning early in a project and continues through completion. It is a planning and scheduling function and should involve project management, stakeholders, design, cost and scheduling, and procurement. Typically, this is done at the preconstruction phase. If done properly, the team will account for equipment delivery first (as this usually has the greatest impact on overall project schedule) and then phase in the various construction packages (underground, foundations, building erection, mechanical, electrical and plumbing trade packages, controls, voice/data/security, etc.) as required to complete the project. This planning is paramount to good overall execution and should be revisited continually during the execution of the project.

Procurement Matrix – this should be a comprehensive list of the equipment and subcontract packages that are defined above. The equipment purchasing package typically uses the equipment list as its backbone. The procurement matrix should be broken out as two documents: equipment procurement and subcontract procurement. This matrix shows the package description, package owner, sourcing strategy (competitive bid, sole source), approved (qualified) suppliers, Request for Proposal (RFP) dates, order status (out for bid, awarded, in progress), Recommendation for Award (RFA) responsibility, engineering drawing (reviews, approvals, return) responsibility, expediting responsibilities and status, milestone payments, commitment and expediting schedule and inspection (shop and Factory Acceptance Testing (FAT)) responsibilities and status. The PEP should establish the key responsibilities of this matrix and communicate them to the overall team. The PEP also establishes the overall responsibility of the procurement lead to own the matrix going forward and the obligation to hold weekly procurement meetings to continue to update this matrix as the project goes forward.

Resource Planning

Within the PEP, there should be a document that defines the expected participation of all team members. Using the project schedule and planning from key team members, it is best to break the project down by week and plan the participation of team members. This is typically accomplished through a large spreadsheet that shows expected durations for all design staff (broken out by discipline or role on the project), project scheduling and controls personnel, project procurement staff, preconstruction personnel, and construction personnel as required. Again, the PEP will "right size" this staffing plan based on the overall scope of the project, user group participation, project management, project engineering, design, procurement, project controls, construction, commissioning, and validation. The goal is to schedule the resources in advance and build in the steps to secure the resources. Note that this is not a Roles and Responsibilities (RACI) diagram, which serves a different purpose. The resource planning document secures the resources for expected durations and should assist project controls personnel in predicting professional services budgets. In addition, the resource planning document also should address all phases through construction and qualification. This can only be completed after the design schedule and other contracted services are awarded and properly budgeted.

Roles and Responsibilities

There are many different roles and responsibilities on any given project, varying with the project's size and scope. It is important that the primary roles and responsibilities are defined early on in order to facilitate good communication among team members and promote ownership as the project moves forward. It is a good practice to include a RACI diagram to an appendix of the PEP. The RACI diagram defines who is as seen in Figure 4.

- R=Responsible (who completes the work or task)
- A=Accountable (who is ultimately accountable for the correct completion of the work or task)
- C=Consulted (whose opinion is sought during the completion of the task)
- I=Informed (who is informed or kept up to date on the status of the task or work)

Design Plan

After project scoping and planning, the PEP should focus on the design of the new process, facility and/or site. The following are the key elements of design that should be covered within the PEP:

- Scope of services and design deliverables – the scope is key (as discussed above), but it is important to also cover in detail exactly what deliverables are expected and agreed upon.
- CAD coordination – this is a large topic in and of itself, and it is an important one. The following are some essential elements of CAD coordination that must be clear to the team going forward:
  - CAD platform and version
  - CAD standards, procedures, and conventions
  - Drawing numbering standards
  - CAD deliverables:
    - > 2-D schematics
    - > Piping and Instrumentation Diagrams (P&IDs)
    - > Isometrics
    - > Orthographics
  - Project closeout requirements – drawing turnover requirements
- Design schedule – not just the overall schedule but dates of important reviews, meetings, and other coordination activities
- Design standards to be employed
- Review of design team's role in the document management team
- Review of design team's role in procurement:
  - Bid package/drawing package division
  - Pre-bid meeting attendance and responsibilities
  - Shop drawing review and approval responsibilities
- Construction support responsibilities and duration
- Estimate responsibility, accuracy and plan for the execution of the overall project estimate
- Technology or information management plan – described software and other electronic tools to be used in the execution of the project
- Health, safety, and environmental planning
- Value enhancement – this is primarily focused on value engineering. The design plan should discuss the value engineering expectations of the project as well as the manner in which ideas are documented, evaluated and incorporated into the design.

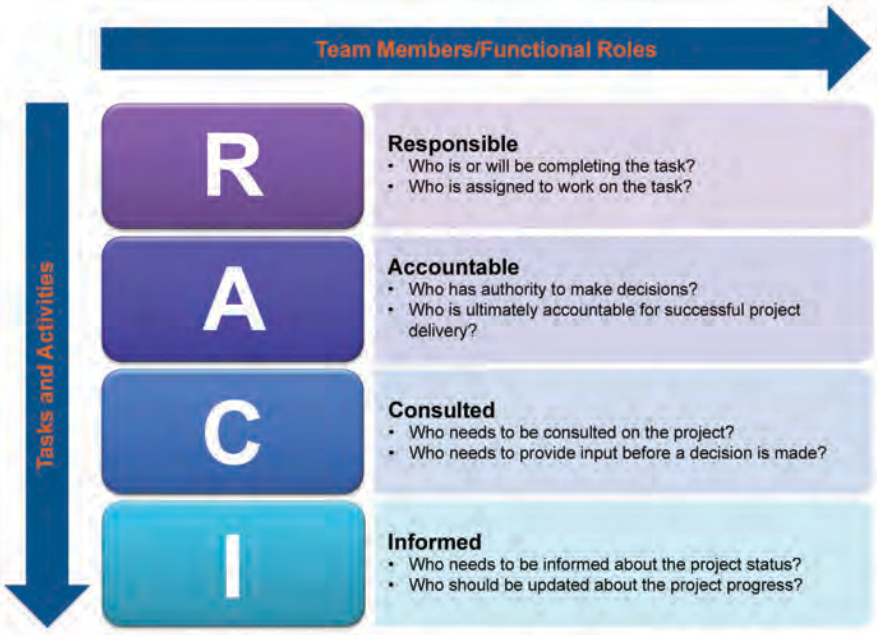

Figure 4. Typical project RACI chart.

Project Controls Planning

Project controls planning assists the project team in providing the cost and scheduling tools necessary for maintaining the schedule and managing the approved budget. The cost engineer will be responsible for establishing control budgets, monitoring progress, policing discipline productivity, identifying and documenting any changes in a timely and cost effective manner, and forecasting final costs. This project controls function is initiated during the early design and preconstruction phases of a project and follow on through construction, qualification and validation of the project. Project planning involving the

establishment of "estimates to complete," earned value reporting and other elements of project controls should be followed from the beginning of the project until completion.

Key elements of project controls include:

Cost Reporting – the following are recommended examples:

- Monthly (weekly)* project cost report
- An overall resource plan by month (week)*
- Detailed change order log of all change orders indicating status – approved, pending, rejected, void, or under development. This log should be kept current and reviewed during the weekly coordination meetings.
- Monthly invoice log, which will track the invoice number, the value of the invoice, submittal date and payment date.

*depends on project size and scope

Schedule/Planning – planning is one of the most important elements in every project. Overall project planning is captured and documented by project controls personnel. Once a schedule is approved, it should be baselined and included within the PEP. Any significant changes in the schedule logic, forecast, etc., will be accompanied with a written description explaining the basis for the change, forecast, etc. Any requested change to the baseline (target) schedule must be accompanied by the proper change control documentation approved by the project manager.

Schedule Status Reporting – an approach for earned value should be considered for all projects whose size warrants. Earned value is an objective project management tool for evaluating project performance and progress. The project's approach to earned value, reporting, and frequency of reporting should be covered within the PEP.

Construction Plan

This plan covers the following:

Roles and Responsibilities – Construction Management Team

While the overall project organizational chart has already been presented, it is important in the construction arena to reiterate roles, responsibilities, and reporting requirements. The management of trade contractors requires that everyone understand their role and who has rank for making decisions and reporting status and concerns.

Construction Organizational Chart

This should be a chart reiterating the roles and responsibilities of outlined above.

Construction Quality Plan

The quality control program is a formal program that consists of inspections, examinations, and tests to ensure compliance with the design drawings, specifications, codes and standards. The program should be administered by qualified personnel and documented in accordance with written procedures.

Quality assurance is a formal program that verifies and documents that all required tests, inspections, examinations and reviews have been performed to ensure that applicable codes, standards, project documents, and specifications have been met.

The construction management team on a project has the complete authority and responsibility to identify quality problems/concerns, investigate them to the extent deemed necessary and to initiate, recommend and/or provide solutions to those problems/concerns. In addition, it has the authority to cause any activity which is not being performed in strict accordance with the project engineering drawings and specifications, regulatory code requirements and/or the quality control/quality assurance manual to be stopped.

Safety Program and Safety Incentive Plan

The master safety plan communicates the requirements and culture for the safety side of the project. Safety is most important component of every project. Companies have a moral responsibility to do all that they can to ensure that every employee returns home to his or her family as safe as they were when they reported to the jobsite.

The safety plan should incorporate the following elements:

- The role (if applicable) of the safety plan for all contractors/subcontractors and the need for it to be included as a part of trade contracts issued
- Drug and alcohol test and safety orientation requirements for all personnel
- Consideration of safety awards and incentives for superior safety performance by individual subcontractor employees or crews
- Establishment of regular safety audits, inspections, and ratings of performance for each of the subcontractors
- Use of tracking programs, which will allow analysis of each subcontractor's performance, compilation of statistics for historical use, trend analysis, and graphical communications of safety metrics
  - Mandatory utilization of daily toolbox meetings and Safe Plan of Action (SPAs) by trade contractors. Contractors shall prepare SPAs for each unique activity and thoroughly review the SPAs prior to the start of performing that activity.
  - A near-miss reporting program. A near miss is an event that did not cause injury or property damage, but had the potential to do so. An example is tripping

without getting hurt. The goal is to communicate that near misses should be reported immediately in order to prevent a similar incident from causing an injury.

- An unsafe conditions reporting program. All unsafe conditions should be corrected immediately and reported to project management. Permitting requirements for the following activities:
  - > Construction
  - > Hot work
  - > Excavation
  - > Roof access
  - > Crane
  - > Scaffold
  - > Line breaking
  - > Potable water connection
  - > Safety reporting for total construction hours worked, and the number of near misses, first aids, recordable, and lost time incidents

Site Logistics Plan

A site plan drawing should be created that shows directions to the site, proper locations for craft parking, material laydown, dumpster locations, shelter and muster locations, restroom and water locations, etc.

Commissioning and Validation Plan

Sometimes termed the Validation Master Plan (VMP) or commissioning plan, this plan should be referred to within the PEP, but should not be the primary focus. Proper planning and input should be given to the definition of turnover systems, and enough engineering and design should be complete to provide a solid basis for system turnover decisions. Initial activities include a planning session with owner's site representatives to ensure an appropriate system definition and turnover sequence that facilitates a smooth transition into the owner's care, custody and control.

New Collaborations between Manufacturers and Construction Firms

The PEP should be completed as early as possible. For complex projects, such as pharmaceutical facilities, there needs to be complete alignment between the earliest capital planning stage and actual, on-the-ground construction processes. Outdated workflows – in which parties are brought onboard even in late stage construction and where alignment is sought as the project unfolds – are no longer viable. Successful firms are developing a more comprehensive system, tying their construction services in with a process which integrates overall project planning, design, procurement and construction to create cost-effective capital solutions. Firms which assemble an inter-disciplinary team in-house can provide solutions at a project's earliest stages, and are therefore able to provide their clients with a guaranteed project cost from the outset.

Front-end planning, as a series of structured processes, is receiving much industry attention because it provides owners with a formal approach for developing and executing their capital projects, which require long-term investment to develop, build and maintain. Capital project delivery processes and front-end planning have been extensively studied by the Construction Industry Institute (CII). CII is a consortium of more than a hundred leading owner, engineering-contractor, and supplier firms from both the public and private arenas, and its mission is to improve the cost effectiveness and sustainability of the capital facility project life cycle. CII research has shown the critical importance of effective front-end loading to increase project predictability in terms of cost, schedule, and performance metrics. The process conclusively fixes the project scope while capturing design, construction, and operating requirements.

The Total Project Delivery Toolkit

CII has developed a scope readiness tool, the Project Definition Rating Index (PDRI), which is a weighted scoring system that evaluates all aspects of a capital project. The PRDI was developed based on research of more than 25,000 completed capital projects, and it improves the front end planning process and aligns team members' and owner's expectations.

PDRI documents define the key elements of an industrial facility project and provide a rating system for those elements. After the preconstruction team assigns a rating to each of the elements on the checklist, a final score is generated. This score indicates, at a glance, the overall risk associated with a project; during the CII validation process, projects scoring less than 200 (out of 1000 total points) were found to be, according to the CII, "significantly more successful than those that scored greater than 200."

Project Delivery: One Firm's Experience

Using PRDI as a springboard, O'Neal, an integrated design and construction firm, has developed a preconstruction approach that is driven by their proprietary Capital Appropriation Process (CAP). The CAP process can is an assessment tool that can effectively determine cost, scope and schedule for an investment. It provides owners with a thorough front-end assessment of their proposed project and identifies areas in which there is a specific risk to success, especially from a design and cost standpoint as seen in Figure 5.

O'Neal's CAP focuses on project development and delivery models that exhibit the following characteristics:

- Every potential project is viewed as an opportunity for savings.
- Capital is directed toward the areas that best benefit the organization's overall goals.

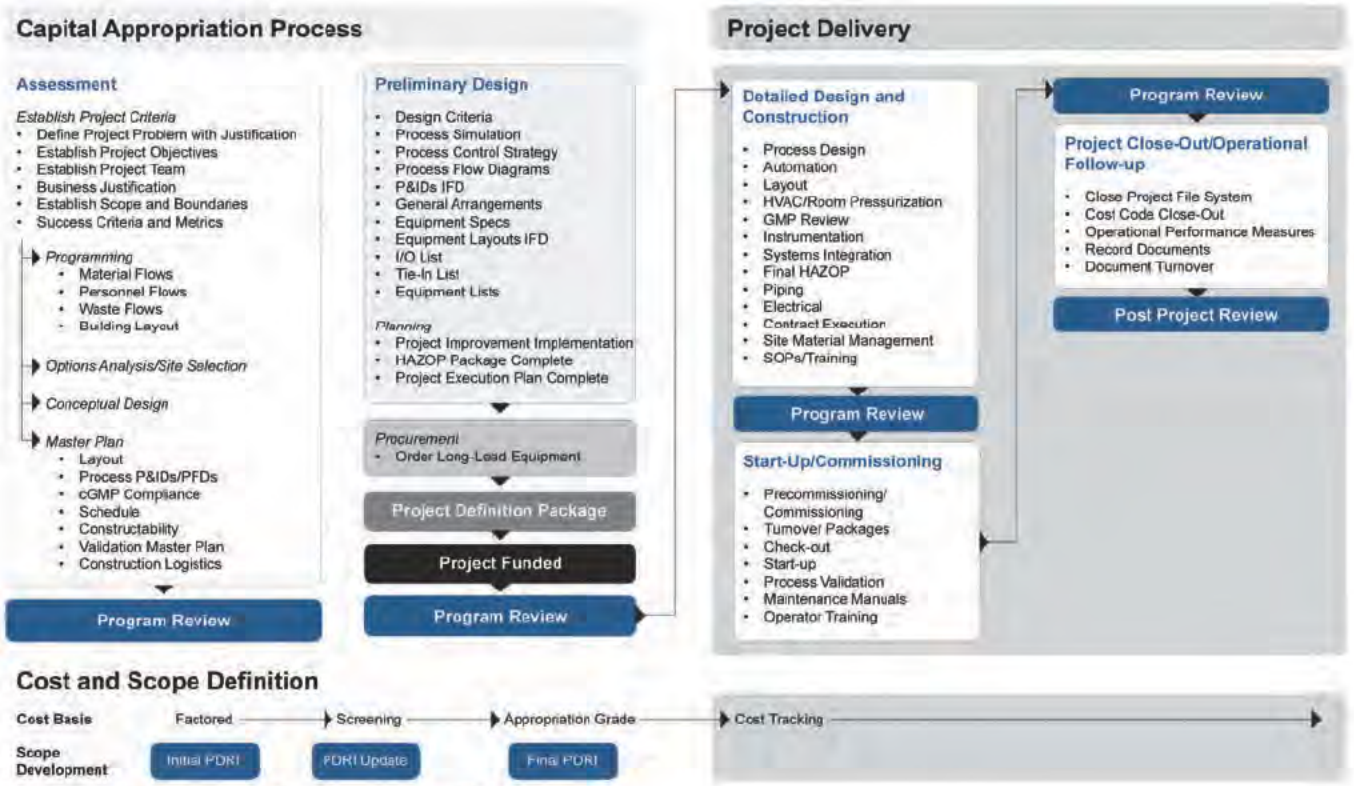

Figure 5. Project development and delivery for cGMP facilities.

- Stakeholders are included in the front-end loading process at the appropriate times.
- Each step in the capital process is connected to and builds on the previous step.
- Long-term requirements are considered at the front-end of a project.
- "Gates" or review processes, occur throughout front-end loading. Projects must meet owner-established criteria at the beginning of the project in order to move forward.

O'Neal has successfully used the CAP and PDRI processes and tools for pharmaceutical, biotech, and other projects, including solid dose manufacturing, aseptic and sterile fill operations, vaccine production, medical device manufacturing, warehousing, packaging and BSL labs.

Proper planning is critical to successful projects in the pharmaceutical industry. The PEP process is instrumental in ensuring effective team communication and interaction. The PEP communicates and documents "the map" for the execution of the entire project, providing guidance over all elements of the project. By setting the tone for effective project leadership, project organization, progress measurement and teamwork, the PEP is a critical tool for successful project delivery. It is important that the project manager issue the PEP early and then take time to review and update the document monthly as the project proceeds to ensure that all of the proper planning is occurring at all phases of project execution.

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About the Author

Robert Garner is in Project Management for O'Neal, Inc. He has a BS in chemical engineering from North Carolina State University and has more than 28 years of experience in capital project management, process engineering, process controls engineering, and production management experience. His primary expertise is in biotech/ pharmaceutical process engineering, fill/finish, and other sterile manufacturing projects. He can be contacted by phone: +1-919-840-9500 or by email: rgarner@onealinc.com.

O'Neal, Inc., 3000 RDU Center Dr., Suite 200, Morrisville, North Carolina 27560, USA.

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Construction Practices: Contamination Risk Reduction within Ongoing Operations

by Charles Hammond and Steve W. Van Wormer

This article presents good construction practices for work in existing pharmaceutical facilities and encourages further development of construction procedures to prevent product safety issues.

Pharmaceutical manufacturers with facilities in mature markets, such as the United States and Western Europe, have faced varying project implementation conditions as a result of increased emphasis on using existing facilities versus developing greenfield sites. Factors such as economic volatility, relocating manufacturing to emerging markets, changes and improvements to manufacturing efficiency, and outmoded facilities and equipment have contributed to the shift in greater utilization of existing facilities.

Many best practices in engineering and construction developed during the industry's expansion on greenfield sites have been slow to adjust to the differing risks when construction takes place next to active production and shares existing infrastructure. Construction practices implemented in Greenfield conditions, where there is little or no impact on existing operations, do not typically contain the standard of care and rigor that are necessary when working in existing operations.

Significant attention and focus have been given to the best engineering and validation practices in the pharmaceutical industry, while less focus has been given to the methods of construction. Ongoing, large capital investments by the pharmaceutical industry have allowed engineering firms to gain vast experience, and along with owner's input, lead to the development of engineering practices and solutions targeting the project's completed performance. Engineering processes and procedures are objectively defined and similar, if not shared, by firms across the life science industry. Consistent application of these good engineering practices makes the final physical outcome of the project predictable.

During the key implementation phase; however, construction project execution has not evolved into industry-wide or generally accepted defined processes, procedures and methods to the same degree. Lack of these practices is evidenced by the "surprising frequency" of construction as a source of contamination as reported by the FDA.[1] Good procedures and practices to control construction activities and its byproducts represent a significant opportunity to minimize the risk, if not eliminate, such outcomes.

The increasing percentage of pharmaceutical construction projects taking place within existing facilities, adjacent to ongoing operations, creates significant vulnerability of contamination caused by construction. This can be disproportionately detrimental and extremely costly if manufacturing's work-in-progress is affected, even if the initial capital investment or project budget is not that large.

This lag in the development of construction practices tailored to prevent such issues during renovations may be attributed to traditional engineering practices that do not take means and methods of construction into account. Also, the means and methods needed to construct within an operational pharmaceutical facility are not typically included in construction management curriculum. Rather, construction professionals have to rely heavily on acquired practical experience and exposure to different project environments. Engineering methods, on the other hand, are well shared

through engineering curriculums, industry organizations, and migration of pharmaceutical professionals from one company to another.

Here, the objective is to define currently utilized good construction practices for projects in existing pharmaceutical facilities and to encourage further development of construction procedures to prevent contamination and product safety issues.

Project Life Cycle

The level of effort and extent of practice or procedure definition varies through the project life cycle, usually commensurate with the level of development of detail around the scope of the project. Construction management tasks throughout the life cycle focus on impact and risk identification, from business planning to project closure. As the project moves toward closure, the activities focus on prevention, planning and execution. There are tasks at each life cycle phase that help mitigate risks related to construction. This article is formatted to identify construction management related tasks at each stage of the project life cycle. A "pass gate" approach at the end of each life cycle phase is recommended to ensure that there is no impact by construction and that product safety remains intact.

Business Planning

In response to growing pressures to improve growth and margins, pharmaceutical manufacturers are striving to:

1. Increase research and development productivity, including innovation needed for new drug development
2. Respond to currently untapped or unmet medical needs, particularly due to the increasing prevalence of chronic diseases in aging populations and those with unhealthy lifestyle choices
3. Expand market share to growing populations in developing countries

Concurrent with these activities is the requirement to create, consolidate and maintain pharmaceutical manufacturing facilities that are efficient, technologically cutting-edge, and able to develop products with the highest quality and safety standards in mind.

The owner must involve their operational personnel from the start of the project to ensure that the proposed option will work within the available space and determine any high-level impacts from an operational perspective.

For construction management, the company and selected construction management team must have the experience

and background of doing work in a controlled environment, as well as training specific to the site's access and containment requirements. This knowledge is critical for the team's input on estimating, logistics planning and scheduling, in addition to overall project success.

A high-level construction logistics plan should be developed during evaluation of site selection alternatives during the business planning phase. Physical layout of an existing facility and availability of area contractors could impact site selection alternatives and Rough Order of Magnitude (ROM) estimates at this phase, so early evaluation is necessary. See Figures 1 and 2 for examples of high-level logistics plan reviews.

This high-level plan considers the logistics of selective demolition – for instance, controlling the removal of debris to prevent contamination. Assessment of existing building space without considering construction logistics could fail to discover that the work area is not accessible without construction and operations crossing paths. This can be extremely costly if the area of work is completely surrounded by operational areas that must continue to function. This scenario could later lead to product risk and create additional mitigation costs beyond what was planned for in the contingencies of a ROM.

Many large pharmaceutical construction projects are occurring on sites where a significant project has not taken place in years. A construction project within a pharmaceutical environment needs to be both managed and constructed by knowledgeable and well-trained personnel. The business planning phase should include evaluation of the availability of trained contractors and required training for new contractors. Costs for traveling or specialty contractors need to be included if there are not sufficient contractors that are local or experienced with the facility. Budgets for training programs also should be established at this phase.

Facility Planning, Design, and Preliminary Engineering

The overall space requirements should be considered during *programming*. As these requirements are defined and preliminary engineering takes place, the construction logistics plan can be developed.

Requirements from operations for both the design as well as the logistics during construction must be determined at this phase prior to implementation. Input for access and shutdowns needs to be provided to help define the logistics plan.

The construction logistics defined during business planning will be expanded upon, creating more detail for the actual effect of construction on adjacent areas and systems. Normally, the project team will define building and user requirements during programming. Figure 3 features a sample of a partial programming questionnaire. In pharmaceutical construction, the same will need to be done for the construction space and process. Schematic or preliminary design follows programming and includes a high-level physical drawing of the area of construction, including planned access routes. HVAC diagrams showing conditions during construction, or each phase of the construction, need to be reviewed for potential impacts on adjacent operations.

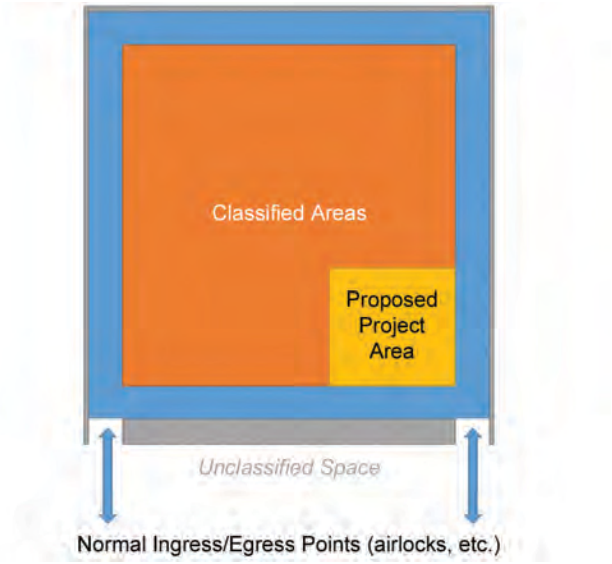


Figure 1. Example high-level logistics review: initial conditions.

The criticality of the project and number of people expected to be working on it drives the number of field-staff

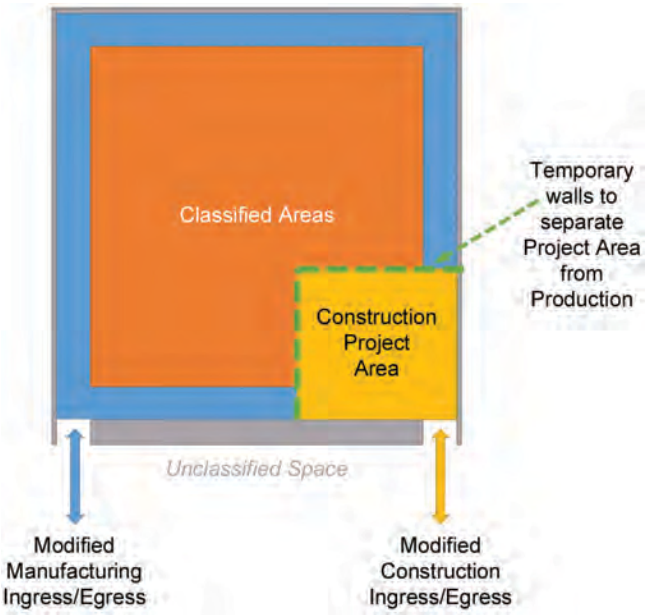


Figure 2. Example high-level logistics review: potential construction conditions.

needed to manage the project; however, subcontractor selection can have a huge influence on the ability to contain any construction impact. If the site or project doesn't maintain trained, knowledgeable subcontractors that regularly work in pharmaceutical facilities, the management team size must be increased and significant training of all subcontractor personnel must be planned before the project starts to maintain product safety. An evaluation of an area's contractors can determine if this is a risk factor for a particular project.

Programming for construction logistics must include:

1. The anticipated flow of construction personnel to and from the worksite, including definition of:
   a. Expected gowning and Personal Protective Equipment (PPE) requirements at different points
   b. Expected containment and isolation requirements for personnel traffic
2. The flow of construction materials in and out of the space, including identification of:
   a. Expected inspection and cleaning points and requirements for incoming materials
   b. Expected containment requirements for outgoing materials; for example, sealed debris containers that are cleaned prior to leaving the construction area
3. HVAC requirements during construction, so that these can be built into the design documents. Many times, HVAC demolition and new installations are phased, in order to:
   a. Separate construction from operations, including the construction pressurization plan
   b. Complete construction modifications
   c. Reconnect the completed construction area to turn back over to operations

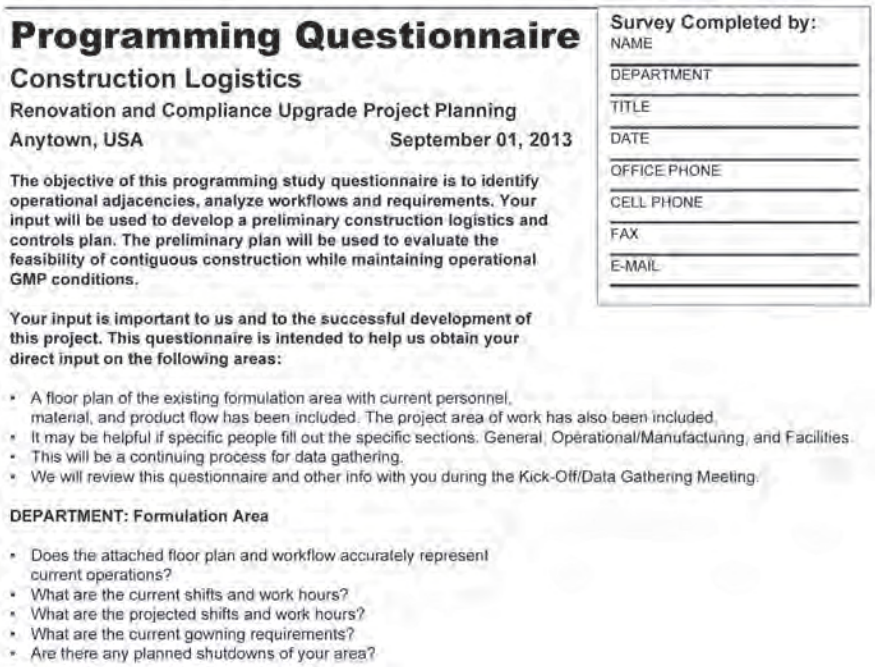
This approach could require three or more sets of drawings showing the work to be completed in each phase, which engineering must anticipate in its planning.

The deliverable in this phase is a written description of the requirements of construction, which allows for project execution without impacting or contaminating adjacent production space.

Design, construction management and adjacent operations members of the project team should thoroughly examine the project description and drawings to confirm that requirements to construct adjacent to operations have been met. In addition, adjacent production schedules should be revisited at this point, to account for changes in production that could impact construction.

Once the above tasks are completed, isolation, containment and construction logistics requirements will have been sufficiently defined to allow for cost estimating and detailed engineering. The budget, or scope of work, can then be adjusted and reviewed to confirm the final site selection and project value. An example of a simplified checklist that can be used to confirm your logistics plan is completed can be seen in Table A.

The level of effort and detail applying these practices will be determined by the complexity of the project and amount of risk to adjacent operations. Tools such as the Ishikawa diagram (fishbone diagram) can be used to help identify risks that need to be controlled - *Figure 4*.



Programming Questionnaire

Construction Logistics

Renovation and Compliance Upgrade Project Planning

Anytown, USA September 01, 2013

The objective of this programming study questionnaire is to identify operational adjacencies, analyze workflows and requirements. Your input will be used to develop a preliminary construction logistics and controls plan. The preliminary plan will be used to evaluate the feasibility of contiguous construction while maintaining operational GMP conditions.

Your input is important to us and to the successful development of this project. This questionnaire is intended to help us obtain your direct input on the following areas:

- A floor plan of the existing formulation area with current personnel, material, and product flow has been included. The project area of work has also been included.
- It may be helpful if specific people fill out the specific sections. General, Operational/Manufacturing, and Facilities
- This will be a continuing process for data gathering.
- We will review this questionnaire and other info with you during the Kick-Off/Data Gathering Meeting.

DEPARTMENT: Formulation Area

- Does the attached floor plan and workflow accurately represent current operations?
- What are the current shifts and work hours?
- What are the projected shifts and work hours?
- What are the current gowning requirements?
- Are there any planned shutdowns of your area?

Survey Completed by:

NAME

DEPARTMENT

TITLE

DATE

OFFICE PHONE

CELL PHONE

FAX

E-MAIL

Figure 3. Programming questionaire.

Detailed Engineering

During detailed engineering, the design is completed with full detail to allow the project to be accurately bid and constructed.

In addition to standard engineering documents, the design documents for pharmaceutical work must include floor plans showing isolation barriers, sequenced drawings showing HVAC changes for construction pressurizations and final conditions, and utility diagrams reflecting the sequence of construction for demolition and tie-ins. A typical engineering design will have a demolition drawing and a new, finished installation drawing. The utilities sequence is not typically taken into account, as it is considered a means and methods issue to be resolved by construction management in the field. However, the sequence is clearly defined in the scope of work

to support and clarify the isolation sequence and allow for quality assurance planning.

Standard Operating Procedures (SOP) must be referenced, revised or created to address the isolation plan specific to the project. The SOP documents must be incorporated into the scope of work to ensure that bidders and contractors are clear on the requirements for the specific project.

All engineering documents must incorporate material selections and design requirements, providing specific information and two-way communications between the construction team and quality assurance.

Planning After Design Completion

After the design is completed, but before construction begins, the impact assessment should be finalized with appropriate controls planned for the work to take place. In order to maintain adjacent production, enforced shutdowns are often phased to minimize the duration that production areas need to be shutdown. The phases of manufacturing operations to be maintained are critical in deciding the requirements needed.[2]

A logistics plan must be finalized with approvals from quality assurance, operations, maintenance, engineering and construction. The causes and effects of potential contamination must be reviewed and planned for using methods such as an Ishikawa Diagram.[3]

Logistics plan considerations include:

1. Planning and implementation of all personnel routes, gowning and PPE
   a. Example: gowning may be required to be worn to get to the construction area, then removed and new gowning worn to return through classified spaces.
2. Consideration of material ingress and egress, as well as the level of containment required for the materials
   a. Example: when materials pass through a classified area, they may need to be inspected prior to entry and/or put in sealed or enclosed containers that are cleaned.
3. Determination of temporary barrier requirements and locations, and planning for their installation to isolate the construction area from production
   a. Example: temporary walls may be constructed of a simple plastic curtain, or may need to be more rigid and constructed of metal, drywall or plastic and caulked in, due to potential damage or pressurization requirements.

Construction Separation/Logistics Checklist		Completed?	N/A?
HVAC modifications and balancing completed to separate construction from operations?			
	Pre-balanced and pressurization checks completed prior to any work taking place		
	Additional filtration or removal of return air from construction area that feeds into operational areas		
	All supply air and exhaust air balanced to keep construction area negatively pressurized to surrounding GMP spaces		
	Balancing & Airflow Diagrams (showing pressurization) checked for compliance prior to re-starting operations and/or construction		
Construction Access defined and separated from Operations?			
	Material/Debris access locations, cleaning and inspection plans in place		
	Personnel access locations, gowning, and PPE plans in place		
	Personnel training plans in place before allowed access		
	Physical barriers in place for each use/classification		
	Changes to operational procedures or additional cleaning defined		
Electronic Disconnections/Shutdowns traced and planned for separation of operations from new construction?			
	All affected feeds defined and planned for modifications		
	All material available prior to modification/shutdown		
Piping disconnections/shutdowns traced and planned for separation of operations from new construction?			
	All affected piping systems defined and planned for modifications		
	All materials available prior to modification/shutdown		

Table A. Construction separation/logistics checklist.

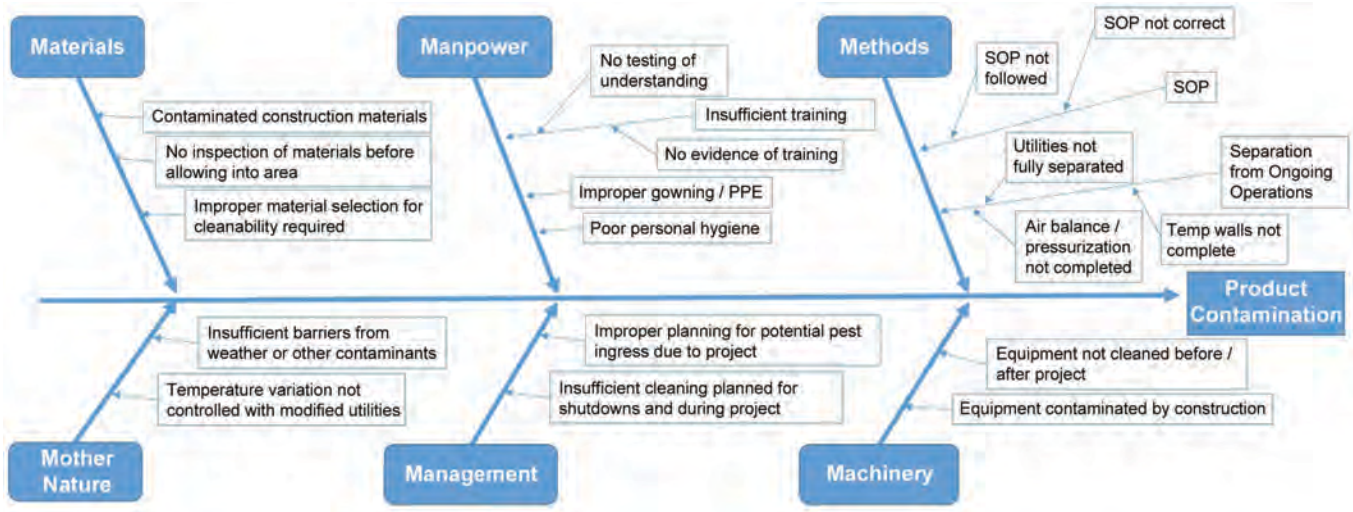


Figure 4. Ishikawa diagram.

Next, finalize all SOPs governing the work to take place, in addition to any modifications to operational SOPs for the surrounding production areas. Finally, determine verification requirements for the construction area and surrounding production areas before work takes place. This could include:

1. Additional particle and/or viable monitoring instituted in surrounding areas to continually confirm that construction is not impacting production
2. Periodic or continual testing of construction area pressurization to ensure that the area stays negative to the surrounding production

If it is possible to physically access the area of work, the final design documents should be fully reviewed in the field to ensure that the existing conditions match the planned design. A construction project's contamination plan and overall project plan can be completely derailed if unplanned issues exist that were not fully realized until after work begins. If unplanned systems are accidentally modified or changed, product contamination could result.

By following the steps outlined and defined in the business planning, facility planning and engineering phases of the project life cycle above, the phased impact on utilities and timing of shutdowns should be well understood, and can then be planned for work completion.

Project Execution

Once the design, logistics and appropriate containment plans are in place and fully approved by quality assurance and operations, the project can start.

Prior to the work taking place, each individual worker must be trained on all SOPs and routes for construction. This could include different routes and containment plans for each phase of construction in a multi-phase implementation. Emphasis on minimizing bio-burden, both during shutdowns and construction, must be fully understood by every worker.[4]

The importance of this is highlighted by a 2005 case study from the *PDA Journal of Pharmaceutical Science and Technology*, where it was reported that contaminants discovered in media fill vials had migrated from the area of construction activity.[1]

Particularly in a pharmaceutical environment, it is crucial to understand and remember the bigger picture and broader implications for protecting the people, products and property. The whole job site should be regularly reviewed for any hazards that could potentially cause ingredient or product contamination, research animal disturbance, product manufacturing disturbance, production delays that could affect ingredient lifespans and quality, or any other issues that could possibly harm the manufacturer's product quality or reputation.

The following are examples of items that must be completed at the start of work:

1. All systems and facilities that will be modified should be pre-tested to confirm that acceptable parameters were maintained while production was underway.
2. Systems that will be modified for construction must be shut down.
   a. Install barriers to isolate the project area from production. Barrier installation must be coordinated with pressurization requirements.
      i. The construction of the barriers varies depending on the level of cleanliness of the adjacent production.
      ii. Example: in classified spaces, it is critical to have barriers that are constructed of non-organic clean-

able materials, are sealed to adjacent spaces, and are sufficiently tamper-resistant to avoid damage that could contaminate adjacent production.

b. Disconnect and isolate systems that will be brought back online for production to continue while the construction takes place. Complete all validation and testing to ensure that these systems are performing within acceptable parameters for production after the modifications.
   i. Example: isolate HVAC branches or systems and re-balance operational areas to their requirements, in addition to the construction area to maintain negative pressure to adjacent spaces for contamination control.

c. Complete cleaning and validation of adjacent areas to confirm that they are back to acceptable levels to return to production.

3. Once the work area is separated, construction can proceed on the project. All previously developed plans and SOPs must be followed to ensure that the work progresses without affecting other areas.
4. At the completion of the project or following each phase, another shutdown of production is needed. Similar steps should be followed to put all systems and utilities into their next or final configuration. All systems and facilities should then have post-testing and cleaning to confirm readiness to return to production.

Field observations completed by *Controlled Environments* identified an organization faced with cleanroom start-up delays following a construction shutdown, because Streptomyces bacterial spores were found even after triple-cleaning the facility.[5]

Cleanroom processes must be successfully cleared at each stage of construction before products are able to move on to the next stage. Closely monitoring cleanroom sterility at all stages will help ensure product quality and safety.

Project Closure

At the completion of the construction work, after the final shutdown is completed, the new area is turned over to operations for final cleaning. At closure, all documents are turned over to quality assurance for review and approval. Once reviewed and approved, the project is complete.

Case Study: Filling Line Installation

A recent project created a space for a new filling line with Grade-A filling space, inside Restricted Air Barrier Systems (RABS), surrounded by Grade-B personnel space. The new Grade-A/B filling space was adjacent to existing to Grade-C and Grade-D space and built in what was previously controlled-non-classified space. Access to the new Grade-A/B filling space was through controlled-non-classified space

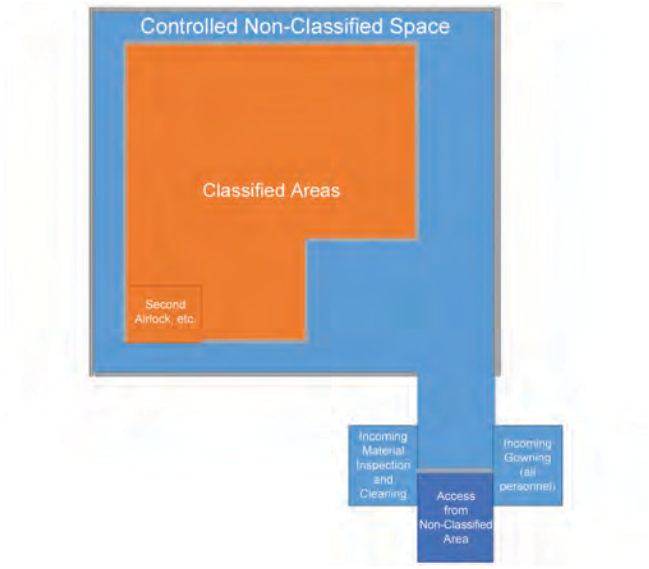


Figure 5. Case Study: existing conditions.

during construction. See Figures 5 to 7 showing the configurations of the space throughout the project.

This particular project required the following:

1. HVAC modifications
   a. Pre-balance and pressurization checks validated the HVAC system for prior production.
   b. Temporary exhaust was installed to keep construction area negative to the surrounding space.
   c. The existing supply, return and exhaust were disconnected from the area.
   d. Operation areas were re-balanced and confirmed for the pressurization of the construction area to return to service.
   e. Complete construction of all new duct and HEPA banks was completed while operations were in production in adjacent spaces. The new systems don't connect to existing systems at this stage.
   f. One final, short shutdown was needed to connect and startup the new equipment to bring the space into use. Final balancing and pressurization was completed to turn the area over to operations for use. Smoke studies and equipment testing were able to take place post-construction.
2. Construction Access
   a. Material Access and Egress
      i. Incoming materials were required to be inspected, cleaned and wrapped at the in-going material airlock to contain anything being dropped while moving through controlled-non-classified areas.
      ii. Outgoing debris and excess materials were inspected, cleaned (or placed in carts that had their exterior cleaned) and wrapped at the temporary construction

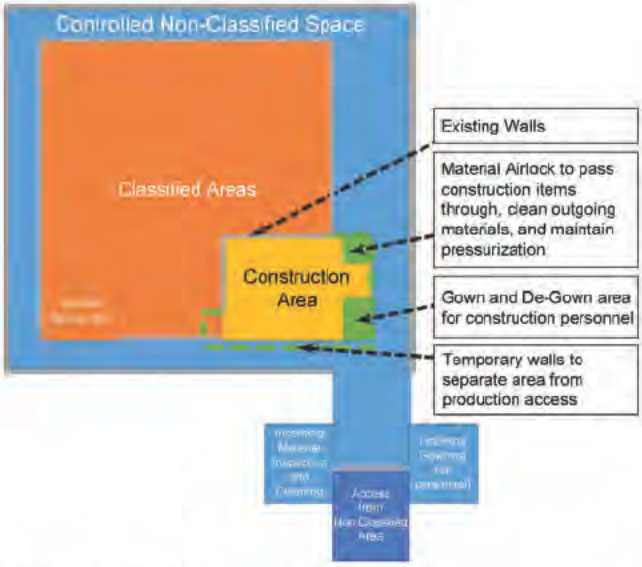


Figure 6. Case Study: construction conditions.

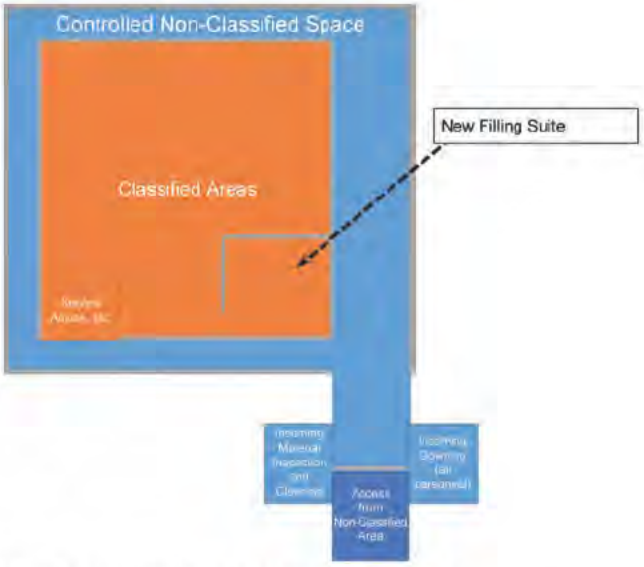


Figure 7. Case Study: final (turnover) condition.

airlock to contain anything being dropped while moving through controlled-non-classified areas.

b. Personnel Access and Egress
   i. Incoming personnel put on gowning in a similar fashion to operations personnel. The gowning was then removed when they entered the temporary construction airlock.
   ii. PPE in the construction space followed standard OSHA requirements for the work being performed.
c. Personnel Training
   i. All workers went through training covering all of the containment and construction requirements for the project. This was led by operations with workers tested for understanding at the completion of training, before starting work.
d. Temporary Walls
   i. At all points where the work area joined to classified spaces, walls were constructed of metal studs, plastic sheeting and caulked hard-plastic for damage protection and cleanability.
   ii. At all points where the work area affected the controlled-non-classified space, a metal stud and plastic sheeting wall was constructed for pressurization. Plastic sheeting was installed on both sides to minimize the effect of small amounts of damage.
   iii. To create construction area airlocks (both personnel and material-pass-through) inside the construction footprint, a metal stud and plastic sheeting wall was constructed to control contamination migration from the construction area.
   iv. All activities that created a large amount of particulates in the construction area were required to drape plastic sheeting around their specific area to minimize migration of dust particles even inside the construction space.
e. Cleaning Requirements

   i. Operations reviewed the impact of the additional personnel and material traffic through their access points. They increased the frequency of floor cleaning and wipe downs around the construction area.
   ii. Construction was required to clean both the material and personnel airlock multiple times daily.
3. Electrical System Changes
   a. Power feeds were reviewed on the site to confirm their impacts prior to starting work.
   b. New work was installed as much as possible to prepare for the shutdowns.
   c. Affected electrical systems had shutdowns coordinated with operations to allow for modifications to the electrical system.
4. Piping and Utility Changes
   a. Each of the many utilities that were installed for this project (water for injection, purified water, pharmaceutical nitrogen, etc.) were verified in field for their actual existing condition to confirm plans for shutdowns.
   b. New work was installed as much as possible to prepare for the shutdowns.
   c. Each utility had a shutdown to tie-in the new systems and reconfigure the existing systems as required.
5. Summary of Case Study
   a. These practices listed in this case study allowed construction to complete while operations continued in adjacent space. With the additional controls and procedures, no contamination or product issues occurred. The shutdown of operations was limited to two short operational stoppages for separation and reconnection of the space to operational areas.

Conclusion

This article outlines and defines practices to be followed to minimize risks during construction in an active pharmaceutical environment. These steps allow for planning and input from the appropriate parties to account for additional actions that are needed for pharmaceutical construction. As the project progresses through the life cycle, the level of detail increases until the project is finalized and fully approved for project execution. This allows all parties to understand and follow the strategy that is in place to avoid risk of product contamination.

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About the Authors

Charles (Chas) Hammond, PE is Senior Project Manager for The Austin Company. Hammond holds a Bachelors in construction engineering and a Masters in engineering management from Western Michigan University. He has more than eight years of experience in constructing cGxP validated spaces within existing facilities for different classifications and products. His knowledge includes construction of wet and dry pharmaceutical product areas for human and animal health, including potent drug manufacturing and BSL-3 lab construction. Hammond has experience as an engineer, program manager, project manager, and construction manager on construction and design-build initiatives at multiple manufacturing facilities. He can be contacted by email: charles.hammond@theaustin.com.

The Austin Company, 9764 Portage Rd., Portage, Michigan 49002, USA.

Steve W. Van Wormer is General Manager and Manager of Construction for The Austin Company. Van Wormer is responsible for the planning, supervision, and coordination of the Michigan office and Construction Services operations, including Austin's commitment to schedule, cost, and quality. He has more than 18 years of experience managing construction activities within pharmaceutical production environments, including project and construction management, in addition to various roles, including safety director, superintendent for environmental projects, and maintenance superintendent. Van Wormer received training from ISPE, AMS Management Consultants - Capital Project Management Process, and Eastern Michigan University - Occupational Safety and Health Standards for the Construction Industry. He can be contacted by tel: +1-269-760-6019 or email: steve.vanwormer@theaustin.com.

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High Purity Process Piping: Harmonization of ASME Codes and Standards

by Barbara Henon, Vince Molina, Richard Campbell, and William Huitt

This article presents interactions between the ASME Bioprocessing Equipment (BPE) Standard and ASME B31.3 Process Piping Code Committees following the addition of Chapter X High Purity Piping to the 2010 Edition of B31.3. This collaboration of ASME Committees will help to assure both safety and cleanability of high purity piping systems.

Following the introduction of the ASME Bioprocessing Equipment (BPE) Standard in 1997, most new pharmaceutical and biotechnology plants around the world have been constructed using the ASME BPE Standard.[1,2] The original scope of this standard, as approved in 1989 by the ASME Council on Codes and Standards stated:

"This standard is intended for design, materials, construction, inspection, and testing of vessels, piping, and related accessories...for use in the biopharmaceutical industry."

The ASME B31.3 Process Piping Code also includes piping in pharmaceutical plants as being within its scope.[3] The BPE Standard references ASME B31.3, but there are inherent differences between the two ASME documents that have only recently been addressed. While the focus of the Code is primarily on safety issues, the 2010 Edition of ASME B31.3 introduced a new chapter, Chapter X *High Purity Piping*. Chapter X covers piping in high purity industries including the semiconductor and bioprocessing industries that have a particular need for cleanness and/or cleanability of their piping systems, but also must meet the safety requirements of the Code.

Although the ASME B31.3 Code and the ASME BPE Standard have been developed independently, it is important going forward that they do not contradict or conflict with one another. The addition of Chapter X is an essential first step in closing the gap between the requirements and intent of the ASME BPE Standard and the Code. Even before the publication of Chapter X, members of both ASME Committees have been working together to harmonize the two ASME documents for which the latest editions of both are 2012.

High Purity Piping

The need for a chapter in the ASME Process Piping Code to address high purity concerns became apparent in 2004 when an engineer and a member of the B31.3 Code Committee started to write a specification for an Ultra-High Purity (UHP) piping installation using the ASME B31.3 Code. He found that process piping systems typically used in semiconductor plants were not adequately addressed in the Code. This was the case even though the Code identifies piping in semiconductor plants as within the intended scope. The semiconductor industry uses standards written by Semiconductor Equipment and Materials International (SEMI) that reference ASME B31.3.[4,5] The emphasis of the SEMI standards is on cleanness rather than the basic safety considerations of ASME B31.3.

Semiconductor industry practices are based on the requirements of fabrication facilities for UHP fluids that are used in the process tools.[6] Achieving UHP levels of cleanness in fabrication of process gas lines was necessary in order to increase the yield of semiconductor integrated circuits.[7] Gas storage and delivery systems ***must not*** add impurities to the fluids that typically range in purity from 99.9999% to 99.999999% for chemical and particulate contaminants. These gases may be highly toxic, pyrophoric (spontaneously combustible in air) or corrosive. Major advances in fluid handling and fabrication technology were essential to meet the demands for both purity and safety.

Orbital Welding Technology

In the 1980s and 1990s, fabricators in the semiconductor industry began using autogenous orbital Gas Tungsten Arc Welding (GTAW) for joining process gas lines because the smooth inner weld bead resulted in cleaner systems than could be achieved with manual welding. Orbital welding was part of the drive to reduce particulate contamination to very low levels. Welds that are fully penetrated to the Inside Diameter (ID) surface with a smooth inner weld bead are far less likely to entrap particulates than the manual socket welds that were previously used, and cleaner systems were essential to achieving higher product yields.

Ultra-High Purity (UHP) and High Purity (HP) semiconductor piping installations use mostly small diameter Type 316L stainless steel tube, 0.250 inch, 0.375 inch, and 0.500 inch Outside Diameter (OD) rather than pipe. Tube is more suitable than pipe for high purity applications since it is manufactured with tighter dimensional tolerances than pipe, thus increasing the repeatability of automatic welds. Fittings, valves, and other components for semiconductor systems are highly specific to the type of application.

Piping systems in other industries covered in the ASME B31.3 Code include piping typically found in petroleum refineries, chemical, textile, and paper plants that, for the most part, consist of metallic pipe installed with multipass manual welds with filler metal added to the weld. Orbital welds on tubing are typically single pass welds with a flat or slightly concave OD profile. Neither automatic orbital welding nor helium mass spectrometer leak testing, commonly used for testing of semiconductor process gas lines, had been addressed by the ASME B31.3 Code prior to the 2010 Edition.

Weld Coupon Examination

The semiconductor industry uses a different type of weld examination from those previously listed in the ASME B31.3

Code. Because of the repeatability of orbital welding and the impracticality of radiographic (or ultrasonic) examination on small diameter, thin-wall tubing, the semiconductor industry uses a quality assurance system of *weld coupon examination* in which sample welds are made prior to and during production at specified times such as the beginning and end of each shift, and after a change of power supply or purge gas source, etc. The weld coupons are sectioned (cut open) and examined visually for full penetration, discoloration, alignment, cracking, porosity and other specified defects. If a defect is found, previous welds are cut out and production welds discontinued until the weld problem has been identified and eliminated.

ASME Bioprocessing Equipment (BPE) Standard

In the mid 1980s, mechanical contractors in the emerging bioprocessing industry began to use the same fabrication technology as the semiconductor industry. Repeatable smooth welds are essential to assure the cleanability of bioprocess tubing systems to limit or minimize the growth of microorganisms in bioengineered pharmaceutical products. The initial impetus that eventually led to the development of the ASME Bioprocessing Equipment (BPE) Standard was bioprocessing equipment imported from Europe that had manual welds that did not meet the quality standards that were routinely achieved by installers in the United States using orbital welding equipment.

Volunteers working on the ASME BPE Standard committee have helped to systematize the installation of biopharmaceutical process tubing. The Subcommittee on Dimensions and Tolerances specified controlled material chemistry, especially sulfur, to minimize heat-to-heat variability in the weldability of tubing and fittings made from Type 316L stainless steel (and other austenitic stainless steels) and by standardizing the dimensions of weld ends on fittings and other process components to be orbitally welded.

The Subcommittee on Surface Finish set standards for smoothness of product contact surfaces while the Materials Joining (MJ) Subcommittee established weld criteria for product and non-product contact surfaces of orbital tube welds. Acceptance criteria for welds on tubing systems ***do not allow*** cracks, lack of fusion, incomplete penetration, porosity open to the surface, inclusions open to the surface nor undercut. Systems made from nominal diameter pipe are seldom used for the higher purity requirements in the biopharmaceutical industry. If they are used, the welds are made in accordance with ASME B31.3 Table 341.3.2 with additional acceptance criteria of the ASME BPE Standard in which cracks, lack-of-fusion and incomplete penetration are prohibited.

The MJ Subcommittee also established methods of weld examination and inspection that are not used routinely in other industries. The ASME BPE Standard requires visual examination of the outside diameter surface of 100% of tube welds and the use of borescopic or direct visual examination to view the ID of 20% of the tube welds. BPE requires sample welds or coupons be performed prior to production welding and at specified times. Weld logs and weld coupon logs are part of quality assurance with every weld numbered, documented and identified on an isometric drawing or weld map. The ASME BPE is now an International Standard used in 30 countries. The application of the ASME BPE Standard has resulted in very efficient installations of large scale biotechnology facilities such as Amgen, Eli Lilly, Genentech, and others that may have orbital welds numbering in the 30,000s.[8]

ASME B31.3 Chapter X High Purity Piping

A presentation was made to the ASME B31.3 Section Committee in 2005 to point out the gaps in the Code with regard to UHP pressure piping. Permission was obtained from the ASME to begin writing a new Chapter for ASME B31.3. An Ultra-High Purity Piping Task Group (Subgroup H) was formed to examine differences in piping requirements between the practices in the semiconductor and the more established industries covered by ASME B31.3. Since the fabrication practices in the biopharmaceutical industry and the semiconductor industry share commonalities, Subgroup H was expanded to include individuals having expertise in the biopharmaceutical as well as semiconductor industry, and the name was changed to Subgroup H High Purity Piping in keeping with the broader scope.

In writing Chapter X, Subgroup H went through the entire ASME B31.3 Code and identified each paragraph that applied to high purity piping and assembled those paragraphs as well as new paragraphs into the new chapter. Paragraphs in Chapter X have the prefix "U" as, prior to publication, Chapter X was called Ultra-High Purity Piping. Since the term Ultra-High Purity refers to the most critical level of semiconductor cleanliness and has very specific sets of standards that define these requirements, the name UHP Piping was later changed to High Purity Piping so that Chapter X could be applied to a broader range of industries.[9]

ASME B31.3 Fluid Services

Chapter X introduced a new fluid service category, High Purity Fluid Service, to the 2010 Edition of the Code. When an owner designs a piping system to the ASME B31.3 Code, it is his responsibility to select an appropriate fluid service as defined by B31.3. Metallic pipe in the B31.3 Base Code, Chapters I to VI, is typically in Normal or Category D fluid service. Other chapters that were previously added to the code have introduced other fluid service categories such as Category M for piping carrying toxic materials, and High Pressure Fluid Service for piping systems designated by the owner to be in High Pressure Fluid Service. Figure M300

Guide to Classifying Fluid Service is a flow chart provided to help the owner determine the appropriate fluid service for his application.

High Purity Fluid Service is defined as *"a fluid service that requires alternative methods of fabrication, inspection, examination, and testing not covered elsewhere in the Code, with the intent to produce a controlled level of cleanness. The term thus applies to piping systems defined for other purposes as high purity, ultra-high purity, hygienic, or aseptic."*

High Purity Fluid Service can thus include UHP and HP semiconductor process piping as well as hygienic bioprocess piping or aseptic piping for food and diary applications. Piping systems in the chemical processing industry that may require a high level of cleanness or cleanability can be declared high purity by the owner. The owner must declare the system to be in HP Fluid Service and then comply with all of the requirements of Chapter X.[10,11]

Weld Coupon Examination in Lieu of 5% Radiography

Chapter X paragraph U341.4.1 provides for *Coupon Examination* of welds *in lieu of* the required 5% random radiography, ultrasonic, or in-process examination when *orbital welding is used in fabrication*. For the 2012 Edition of Chapter X, paragraph U341.4.1 has been modified to allow coupon examination when *autogenous* orbital welding is used in fabrication or when a consumable insert is used in conjunction with orbital welding.

Borescopic examination is now listed in Chapter X as an approved method of visual examination of orbital welds. This type of examination is effective in detecting both lack of penetration and slight amounts of weld discoloration that are not seen with radiography. Even slight amounts of weld discoloration have been shown to reduce the corrosion resistance of stainless steel and corrosion can have an adverse affect on pharmaceutical products.[12,13]

ASME BPE Fittings Referenced in ASME B31.3

In addition to metallic and nonmetallic face seal fittings used in semiconductor process gas lines, ASME BPE orbital butt weld fittings and ASME BPE hygienic clamp fittings that are used for mechanical joints in biopharmaceutical applications, are now referenced in ASME B31.3.

Hygienic clamp type fittings are mentioned in Chapter X paragraph U306.6 Tube Fittings and also have been listed in ASME B31.3 Table 326.1 Component Standards. Note (3) of

this table refers back to BPE *"Part DT of ASME BPE covers dimensions and tolerances for stainless steel automatic welding and hygienic clamp tube fittings and process components."* In order to be listed, a component must be shown to meet the requirements of ASME B31.3 for structural integrity.

Drawings of hygienic clamp fittings are shown in ASME BPE-2012, Figure DT-2-1, and similarly in ASME B31.3-2012, Figure U-335.8 - *Figure 1*. These clamp assemblies that are used in conjunction with specific types of gaskets, are quite different from the typical flanged and bolted connections used in normal ASME B31.3 piping systems.

In accordance with B31.3 each installed piping system shall be tested to assure tightness. The test shall be a hydrostatic test in accordance with B31.3 para. 345.4 except as otherwise provided. At the owner's option, Chapter X has added helium mass spectrometer testing which is common in the semiconductor industry.

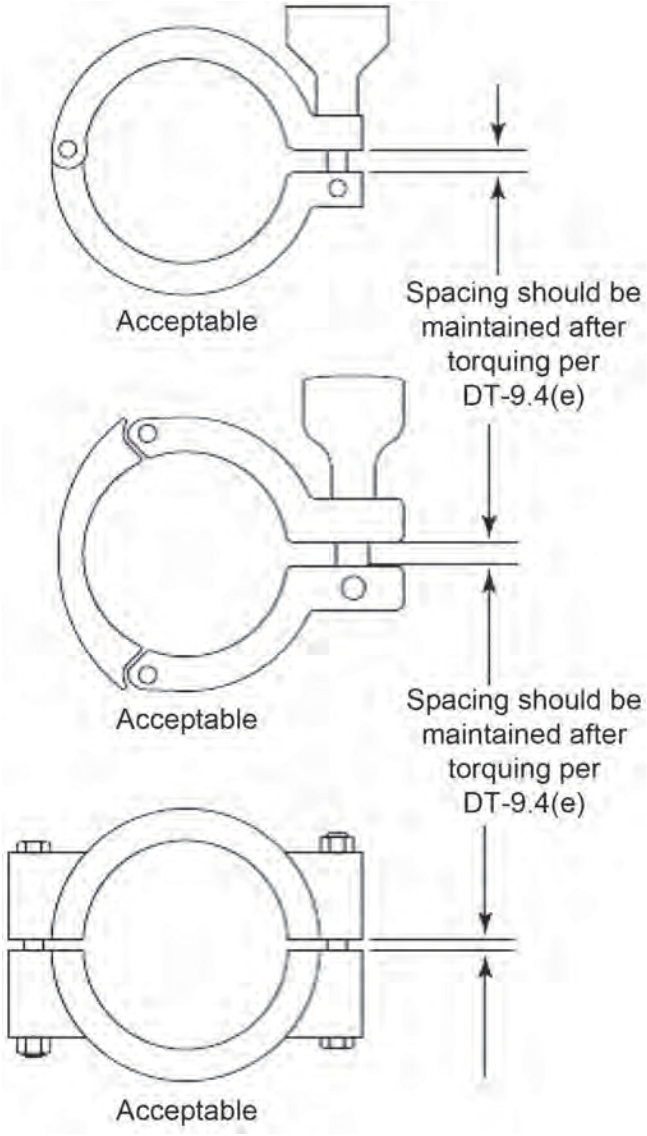

Figure 1. Typical clamp designs used in the biopharmaceutical industry.

When a new term is added to an ASME Code or Standard, a definition more in line with its intended use must be added to the list of definitions in that publication. Definitions were added to ASME B31.3 paragraph 300.2 for *orbital welding, face seal fitting, weld coupon, weld coupon examination,* and *hygienic clamp joint* in the 2010 Edition and a definition of *autogenous welding* was added in 2012.

Harmonization of ASME BPE and ASME B31.3

Interactions between ASME BPE and B31.3 Subgroup H began in 2006 when a member of the ASME BPE Standards Committee and the BPE Subcommittee on Materials Joining (MJSC) attended an ASME B31.3 meeting in Atlanta, Georgia. The Chair and another member of the Subgroup H subsequently were invited to attend the ASME BPE Materials Joining Subcommittee (MJSC) meeting in Philadelphia in October 2007 where the Subgroup H members made a PowerPoint presentation to the MJSC. They stressed the ASME B31.3 emphasis on safety comparing it to BPE's concern with cleanability and control of bioburden. At that meeting, the MJSC appointed an official liaison to interface between the ASME BPE and ASME B31.3 Committees. Since then, liaison reports have been made at meetings of both ASME committees. Other members of BPE have joined B31.3 Committees and these volunteers have worked consistently to bring the two ASME documents closer together.

Many members of the ASME B31.3 Committees were unfamiliar with high purity piping and orbital welding so the members of Subgroup H organized a PowerPoint presentation to the B31.3 Section Committee on this topic in Phoenix, Arizona in 2010. At the same meeting, live demonstrations of autogenous orbital welding were given for all the B31.3 subgroups. Samples of the types of UHP and HP fittings, valves and clamps used in semiconductor and bioprocessing systems, some of which have now been listed in Table 326 of ASME B31.3, were on display.

ASME BPE/B31.3 Harmonization Task Group

Knowing that Chapter X was in preparation, the ASME BPE Materials Joining Subcommittee formed a task group to identify all of the references to ASME B31.3 in the ASME BPE Standard to determine how these references might be affected by the addition of Chapter X to the Code. The Harmonization Task Group met for several years at BPE meetings and reported their activities to ASME B31.3 Subgroup H at their meetings. The task group found a total of 41 references to ASME B31.3 in the 2009 BPE Standard. As

a result, several references in Part MJ in the 2012 Edition of BPE refer to the "appropriate fluid service" which will most likely be High Purity Fluid Service as defined in the 2010 Edition of ASME B31.3 for hygienic systems. References in ASME BPE to specific ASME B31.3 paragraph numbers were changed to general references to ASME B31.3.

A statement was added to the General Requirements section (Part GR-1) in the Scope of the 2012 Edition of the ASME BPE Standard to alert users that for hygienic systems in bioprocessing plants they could now specify High Purity Fluid Service as defined in ASME B31.3. A ballot was approved first by the MJSC then by the BPE Subcommittee on General Requirements (SCGR), but took several attempts for approval by the ASME BPE Standards Committee. These ASME Codes and Standards are by consensus so all comments on the ballots must be answered and all negatives resolved at each successive level of the record. This process works surprisingly well and the negatives are usually constructive with improved wording and clarity the typical outcome. The final, approved reference in BPE Part GR-1 for 2012 is as follows:

> *"This Standard shall govern the design and construction of piping systems for hygienic service. For process piping systems designed and constructed in accordance with ASME B31.3, it is the owner's responsibility to select a fluid service category for each fluid service. Should any fluid service meet the definition of high purity fluid Service (ASME B31.3, Chapter X) it is recommended that such fluid service be selected and the requirements of this Standard and ASME B31.3, Chapter X be met."*

This statement gives ASME BPE the authority to set standards for design and construction of hygienic systems and when a piping (or tubing) system is to be used for hygienic or high purity service that meets the definition of the ASME B31.3 High Purity Fluid Service, that fluid service should be selected. Prior to the introduction of Chapter X, most of these systems were classified as ASME B31.3 Normal Fluid Service. The statement demands that the design and construction requirements of both ASME BPE and ASME B31.3 be met. Thus it is essential that there be no inherent conflicts between the two ASME documents.

Radiographic vs. Coupon Examination

The 2012 ASME BPE Standard (MJ-7.3.3) requires that *"Examinations shall be performed in accordance with the provisions of the specified fluid service in ASME B31.3."* BPE has never required radiographic examination of tube welds. The ASME BPE requirement is for 100% visual examination of the outside diameter surfaces plus a minimum of 20% random borescopic examination of the inside diameter of tube welds while the ASME B31.3 Normal Fluid Service requirement is a minimum of 5% visual examination and 5% random radiography or ultrasonic examination.

Because of the difference in these requirements, there was always some vague concern that BPE requirements were not in full compliance with the Code. However, prior to the introduction of Chapter X, users of BPE and B31.3 who did not specify 5% radiography were not necessarily "violating" the ASME B31.3 Code if they specified *in-process examination* (B31.3 paragraph 344.7) instead of radiography.

With the new Chapter X and by selection of High Purity Fluid Service in ASME B31.3, users of ASME BPE can now perform weld coupon examination *in lieu of* the 5% radiography or ultrasonic examination and be in undisputed compliance with ASME B31.3.

The requirement for 100% visual examination of the outside surface and 20% borescopic examination of the inside by ASME BPE is still in effect for welds in hygienic service referencing the ASME BPE Standard. One could argue that this is a more stringent requirement than the 5% radiographic or ultrasonic examination required by ASME B31.3 Normal Fluid Service.

How Weld Coupons are Made

The semiconductor industry has defined requirements for how weld coupons to be used for weld coupon examination are made and examined. While weld coupons are made to qualify welding procedures (WPS and PQR) and welding operators (WOPQ) to ASME Sect. IX of the Boiler and Pressure Vessel Code,[14] as modified by ASME B31.3, those coupons are used to qualify a range of wall thicknesses, diameters and alloys and may be performed long before construction begins.

Primary weld coupons used for weld coupon examination are made prior to the start of production with sections of tubing of the same alloy, diameter and wall thickness as is being used in production to serve as a quality benchmark for welds made during production. *Production weld coupons* are made during production to assure that the weld parameters from the qualified welding procedure (WPS) and orbital welding equipment continue to result in acceptable welds throughout the installation.

The BPE Standard requires that sample (coupon) welds be made and examined "on a regular basis" to verify that the welding equipment is functioning properly and that the ID purge is sufficient to prevent weld discoloration. Many installers using the BPE Standard make Bead on Pipe (BOP) or Bead on Tube (BOT) welds which are made from a single section of tubing without an actual joint. The members of Subgroup H feel that an actual joint is required for weld coupons made during production, for the purpose of weld coupon examination, to show that the end preparation and fit up of weld components is good enough to result in proper joint alignment. This is consistent with the requirements for

in-process examination as defined by ASME B31.3 paragraph 344.7 where fit up and joint alignment of production welds are checked prior to welding. The next editions of BPE and B31.3 will attempt to clarify and provide more consistent requirements for weld coupons.

Method of Examination

While the procedure for weld coupon examination in the semiconductor industry requires the examiner to section or cut open the coupon for visual examination as seen in Figure 2 top, coupon examination in bioprocess applications may be an indirect visual examination using a borescope, or more likely, a direct visual examination as seen in Figure 2 bottom. A member of ASME BPE MJSC proposed that borescopic examination of coupon welds be allowed by ASME B31.3 *in lieu of* sectioning. This was approved first at the subcommittee level and then by the ASME B31.3 Section Committee and is in effect in the 2012 Edition of ASME B31.3.

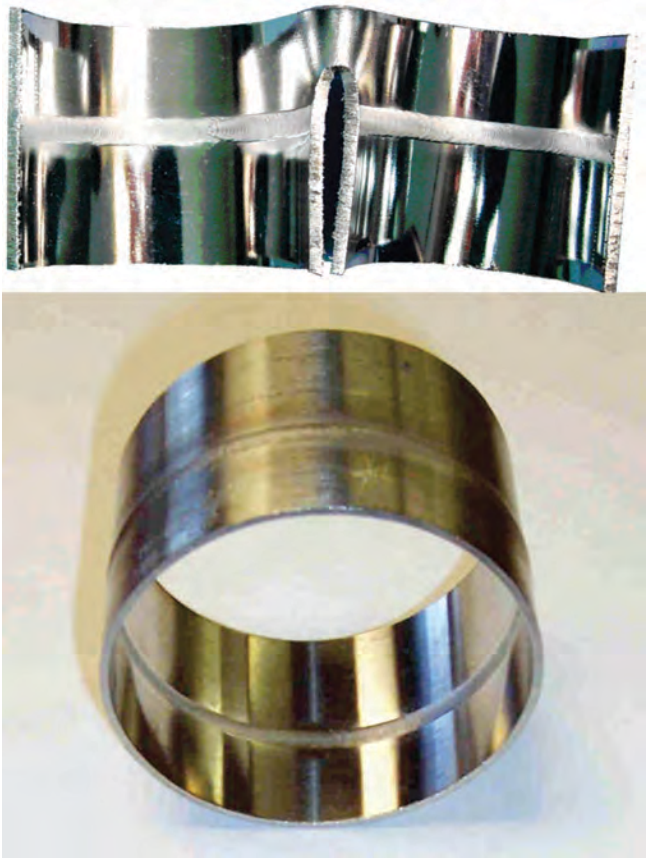

Figure 2. Top: An orbital weld coupon sectioned for visual examination of the I.D. surface for the semiconductor industry. Bottom: An orbital weld coupon made for the biotechnology industry. For High Purity Fluid Service, the welds must meet the acceptance criteria of the referencing code, i.e. BPE or SEMI and also meet the criteria in ASME B31.3 Table 341.3.2.

Acceptance Criteria for Autogenous Welds

Chapter X states that weld acceptance criteria for the referencing code, e.g., ASME BPE or SEMI, shall apply, but welds also must meet the acceptance criteria of ASME B31.3 paragraph 341.3.2. Autogenous orbital welds on tubing generally have a flat OD profile, but may have some OD concavity, especially on heavier wall thicknesses. The BPE Standard makes some allowance for this for tube welds, but refers to B31.3 for welds on pipe. Weld acceptance criteria for B31.3 are based on multipass welds on pipe with the addition of filler wire to the weld, and while they do address OD and ID reinforcement, there is no mention of OD concavity. This is generally interpreted to mean none allowed.

This issue was brought to the attention of the ASME B31.3 Subgroup E, Fabrication, Examination and Testing. This item, to permit some amount of OD concavity on welds made without filler metal, is being evaluated for inclusion in the ASME B31.3 2014 Edition. If approved, this would not only aid in the harmonization of ASME BPE and ASME B31.3, but also will help to extend the use of Chapter X to industries[11] other than biopharmaceutical that reference ASME B31.3 and could benefit from the application of autogenous orbital welding of tubing but might not be able to meet the current B31.3 weld acceptance criteria for OD concavity.

ASME BPE 2012 Edition

The 2012 Edition of the BPE Standard is the first edition of BPE to specifically reference the new High Purity Fluid Service and its associated Chapter X. This edition of BPE has been completely reorganized since the 2009 edition. ASME B31.3 does not address weld discoloration, but the BPE Materials Joining Part (Part MJ) has a new color chart showing permissible and unacceptable levels of weld Heat Affected Zone (HAZ) discoloration for welds on electropolished and mechanically polished 316L stainless steel tubing.

While welding destroys the passive layer and results in some loss of corrosion resistance, the loss can be minimized by proper inert gas purging during welding which limits the amount of discoloration since the loss of corrosion resistance increases with increasing amounts of discoloration.

Acceptance levels for HAZ discoloration were established based on corrosion resistance in the ASTM G150 test and a modified ASTM G61 Potentiodynamic Polarization Corrosion test. At similar levels of HAZ discoloration, the corrosion resistance of welds on electropolished tubing was higher than that on mechanically polished tubing. The techniques and oxygen levels used for the ID purge are detailed in Nonmandatory Appendix M. Previous studies have shown that while passivation can help to restore the passive layer that is damaged by welding it cannot compensate for loss of corrosion resistance caused by poor inert gas purging.[12,13]

Conclusion

The Scope of BPE 2012 has been broadened to say, "*The ASME BPE Standard provides requirements for systems and components that are subject to cleaning and sanitation and/or sterilization including systems that are cleaned in place (CIP'd) and/or steamed in place (SIP'd) and/or other suitable processes.*"

The current scope should open up the BPE Standard to other high purity applications that can benefit from fabrication technology including orbital welding of tubing systems, specialized components, examination and testing methods common to the semiconductor and bioprocess industries, but not previously addressed by ASME B31.3.

By specifying High Purity Fluid Service and using coupon examination of welds in lieu of the 5% radiography or ultrasonic examination requirement of ASME B31.3, users of ASME BPE can now be indisputably Code compliant, and because the scope of BPE has been broadened, the use of BPE should no longer be limited to use by the biopharmaceutical or bioprocessing industry.

There was close collaboration between members of ASME BPE and ASME B31.3 during the development of Chapter X that was published in 2010. This collaboration continued to further implement changes that brought these documents into closer alignment for the 2012 Editions and this work is continuing for the 2014 Editions. This is a classic example of how cooperation between volunteers from two different ASME committees can work together to improve safety standards for piping systems with benefits to both industry and society.

At the Denver meeting of ASME B31.3 in September, 2011, the ASME awarded each member of Subgroup H who had contributed to the writing of Chapter X with a *Certificate of Excellence* in appreciation for their work.

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About the Authors

Barbara Henon is a graduate of Mt. Holyoke College, has an MA in zoology from Columbia University, and a PhD in biological sciences from the University of Southern California. After postdoctoral work in the Division of Neurosciences at the Beckman Research Institute at the City of Hope in Duarte, California, in 1984 she joined Arc Machines, Inc. in Pacoima, California. Dr. Henon helped to develop the Arc Machines Training Department and wrote training manuals

for the orbital welding equipment manufactured by Arc Machines, Inc. Now retired from Arc Machines, she represents Magnatech LLC on the ASME B31.3 Committee. She is the author of numerous articles including *Pharmaceutical Engineering* Article of the Year in 1999. Dr. Henon received the American Welding Society (AWS) Image of Welding Award in the Individual category in 2008. Dr. Henon joined the ASME Bioprocessing Equipment (BPE) Committee in 1989 and served for two terms as Vice Chair of the BPE Standards Committee. She is currently a member of the BPE Materials Joining and Surface Finishes Subcommittees, the Subcommittee on General Requirements and the Executive Committee. Until this year, she was the official Liaison between the ASME BPE and ASME B31.3 Process Piping Committee. This role has now been assumed by Bill Huitt. She is a member of the B31.3 Section Committee and Subgroup H on High Purity Piping that wrote the high-purity chapter of B31.3. She was a member of the Task Force that wrote the SEMI F79 and F81 Standards for orbital welding in the semiconductor industry. She also serves on the AWS D10 Committees and AWS D18 Committees. She can be contacted by telephone: +1-206-546-5518 or email: barbkhen@aol.com.

R.C. International, LLC, P.O. Box 60182, Seattle, Washington 98160, USA.

Vince Molina is a Project Engineering Manager at Air Products and Chemicals, Inc. responsible for managing engineering interface with third party EPC contractors during the execution of Air Products projects globally. He has been involved in piping engineering, design, and construction since 1990 across various industries including nuclear power, petroleum refining, chemical, petrochemical, pharmaceutical, and semiconductor. He has been a member of ASME B31.3 Section Committee since 1992, started as a member of Subgroup A on General Requirements. Molina is currently the Chair of Subgroup H on High Purity Piping which he organized in 2005 to start the development of the new Chapter X that was first published in the ASME B31.3 2010 edition. He can be contacted by telephone: +1-909-447-3976 or email: molinav@airproducts.com.

Richard Campbell is a Bechtel Fellow and Welding Technical Specialist with Bechtel Corporation. With a BS degree in welding engineering from Le Tourneau University and a PhD in materials engineering from RPI, he has worked for 35 years in the welding industry. His work in the high purity industries has spanned more than 15 years and includes owning a welding fabrication shop, a pipefitting union shop, and as an officer with Purity Systems, Inc. a third-party inspection company. Dr. Campbell has been an active participant of the ASME Bioprocessing Equipment (BPE) Standard committee for more than 20 years. He now serves as Chair of the Materials Joining Subcommittee, responsible for welding and inspection requirements. He is also a member of the BPE Standards Committee, Executive Committee, plus several other BPE subcommittees, including the Metallic Materials Subcommittee and was Chair of the BPE Certification Subcommittee for nine years. He is also Vice-Chair of the ASME B31.3 Subgroup E on Fabrication, Examination, and Testing, and is a member of the ASME B31.3 Process Piping Code Section Committee and the ASME B31 Fabrication and Examination Committee. He also serves on numerous AWS codes and standards committees, including the AWS D18 Welding in Sanitary Applications Committee for the food and dairy industry. He is also Chair of the AWS C5C Gas Tungsten Arc Welding Subcommittee. Dr. Campbell is author of more than 20 articles. As an expert in stainless steel welding, he authored AWS's The Professional's Advisor on Welding of Stainless Steels. He can be contacted by email: rdcampbe@bechtel.com.

William (Bill) Huitt is President W. M. Huitt Co. He has been involved in industrial piping design, engineering and construction since 1965. Positions have included design engineer, piping design instructor, project engineer, project supervisor, piping department supervisor, engineering manager and president of W. M. Huitt Co. His experience covers both the engineering and construction fields and crosses industry lines to include petroleum refining, chemical, petrochemical, pharmaceutical, pulp and paper, nuclear power, biofuel, and coal gasification. He has written numerous specifications, guidelines, papers, and magazine articles on the topic of pipe design and engineering. Huitt is a member of ISPE where he was a member of the Task Group on ISPE Water and Steam Systems – Baseline Guide Chapter 10 Rouge and Stainless Steel, CSI (Construction Specifications Institute) and ASME (American Society of Mechanical Engineers). He is a member of the B31.3 Section Committee and Subgroup H on High Purity Piping, a member of three ASME BPE subcommittees and several Task Groups as well as the ASME Board on Conformity Assessment for BPE Certification where he serves as Vice Chair. Huitt is also a member of the American Petroleum Institute Task Group for RP-2611, he serves additionally on two corporate specification review boards, and was on the Advisory Board for ChemInnovations 2010 and 2011 a multi-industry Conference and Exposition. He can be contacted by telephone: +1-314-966-8919 or email: wmhuitt@aol.com.

W.M. Huitt Co., P.O. Box 31154, St. Louis, Missouri 63131-0154, USA.

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The Dirt on Cleaning and Sanitization

by Neil Lewis and Steve Shank

This article presents an overview of the basic concepts and principles of clean design which should be applied when considering equipment and system design.

Historically, chemical processes for both commodity materials and pharmaceutical actives were designed as dedicated processes with no need or thought given to changeover for production of another product. This design approach had a number of advantages, including reduced risk of contamination and adulteration as well as simpler validation. However, in the current business environment of minimal inventory and produce to demand, there is considerable pressure to reduce capital investment by more fully utilizing equipment. This paradigm shift necessitates that a system have the capability to quickly and effectively remove residual product. Effective cleaning, made easier by clean design, minimizes the risk of cross contamination/adulteration, ensures the safety, efficacy, and aesthetics of the product, and protects the process equipment itself. Taking a holistic approach to the design and fabrication of these processes promotes the organization's ability to innovate new products with minimum capital investment; this approach positively impacts the organization's capacity and profitability all while avoiding potential regulatory issues.

It is an interesting dilemma that the majority of equipment used to manufacture Active Pharmaceutical Ingredients (APIs) or Over The Counter (OTC) products is typically designed to be cleaned or rinsed with water. However, the introduction of water into any system brings with it substantially increased risks of microbial contamination. The following quote attributed to Benjamin Franklin helps to highlight the situation:

"In wine there is wisdom, in beer there is freedom, and in water there is bacteria."

The risks of microbial contamination necessitate that the system be designed to tolerate and facilitate some form of antimicrobial process. This process is commonly referred to as sanitization.

This article provides an overview of the basic concepts and principles of clean design which should be applied when considering equipment and system design. The primary focus will be on process systems though the concepts and principles may be applied to other systems and processes.

The fundamental principle, often forgotten in the process of meeting customer or consumer design and operating specifications, is that the ability to be cleaned and sanitized must be designed into the equipment from the outset. It is extremely difficult and expensive to add this capability once a system has been installed; the result is often a virtual rebuild of the system.

When initially looking at any process system from a point of clean design, there are two important concepts and three important design aspects and that must be considered.

1. **Concepts**
   a. Idle Time/Down Time Management - consideration of how to manage the contamination risks when the system is not in use. The FDA reports and summaries often comment on the lack of control during down time.
   b. Contamination Prevention - the elimination of both contamination sources, as well as items that prevent the system from being cleanable, sanitizable, and drainable.

2. **Design Aspects**
   a. Cleanable – the ability to effectively remove the residual product or material from all the product contact surfaces within the system.
   b. Sanitizable – the ability to tolerate predefined antimicrobial treatments intended to minimize the risk of microbial contamination.
   c. Drainable – the ability to completely remove product residues, cleaning or sanitizing media and rinsing agents from the system.

Depending on the specific operation and process, different paths may be taken when conforming to these concepts and design aspects; however, they should be considered and included in the conceptual design discussions and documented in the user specification requirements.

Concepts

Idle Time/Down Time Management

Idle Time/Down Time Management (IT/DTM) is frequently overlooked in many project discussions. IT/DTM is the consideration of how the system is maintained and managed when it is not in use and how it is then brought back into service. IT/DTM is of particular concern in the case of manufacturing biological or pharmaceutical precursor actives with limited shelf life and stability.

There are systems, such as purified water, where the basic design does not allow for any idle time and the system is expected to run 24/7. This is a well-known standard and is often well defined in the process and design definition documentation.

However, the majority of batch processing and storage systems will expect a specific amount of downtime during normal operation based on market requirements, maintenance needs, planning accuracy, and supply chain constraints. The length and nature of any projected downtime must be considered in the overall design. A basic principle to apply in these situations is that of "Clean after Use" and "Sanitize before Use." It is a high risk practice to leave any product residues on equipment surfaces. Over time, oxidation and other chemical reactions will make the material significantly harder to remove. For active materials, the degradation products of these reactions also may have a much higher risk profile than the original material; this could alter both the system design and the frequency of cleaning the process. In addition, prolonged contact of products to the atmosphere can result in significant levels of corrosion on stainless steel surfaces.

The cleaning process also physically removes significant levels of micro-organisms which may have been introduced into the system. Cleaning also deprives any remaining organisms of any sources of nutrition and prevents any significant re-colonization on the equipment. Providing the

equipment is idled or shut down in a clean environment, it would only require sanitization to be ready for future use. Due to the risk of microbial contamination and the inability to store sanitized equipment for long periods of time, the basic principle of sanitize before use is the recommended practice.

The nature of the product also can have an impact on the required frequency of cleaning and sanitization. Compatible products may not require cleaning during changeovers, as it will be possible to push out one material with the next with minimal impact on the following product. The impact of this practice on efficacy, aesthetics, and potential for cross contamination or functionality requires validation, but this is an accepted practice which can reduce the need for cleaning, sanitization and process downtime.

In situations that do require cleaning during product changeovers; however, clean design that reduces both the changeover time and the amount of scrap product is key in assuring the effectiveness of the process. Equally, there are some products, where limited microbial susceptibility may allow cleaning with water between batches. In these situations, clean design is also critical in preventing dilution of the product and subsequent microbial adaptation.

Other questions related to Idle Time/Down Time to be considered in the design include:

- If the system is cleaned or sanitized with heat (e.g., hot water, steam, etc.), how long does it take to cool the system to a temperature acceptable for the process?
- How will the system be protected during cooling?
- Where and how will the effluent from the cleaning and sanitization process be removed from the system?
- What data monitoring systems are needed to control and verify the cleaning and sanitization processes? For example:
  - Pressure or flow monitors on water lines to spray cleaning devices
  - Temperature monitors on supply lines for water used to clean or heat sanitize
  - Temperature monitors on tanks or process lines being cleaned and heat sanitized
- What is done to a system experiencing down time due to a maintenance shutdown?
  - How is the system brought back on line so that the system is not microbially contaminated?
  - How will the system be kept clean and dry?

Prevention

Systems can be designed to eliminate or minimize the need for cleaning and sanitization. This is usually accomplished by either the inclusion of an antimicrobial substance, such as ozone or alcohol, or by designing the system to be continually heated above 65°C (149°F).

However, the addition of preservatives is not considered a prevention strategy. Preservatives are added to provide protection for the consumer after purchase. They are not added to make up for design deficiencies or inadequate Good Manufacturing Practices (GMPs) and procedures.

Preventative strategies are often used for raw materials or intermediates, allowing the need for regular cleaning to be substantially reduced. The most common preventative measures include:

- Keeping purified water systems hot or ozonated
- Terminal filtration of the material
- Installation of micro filters on tank vents (to seal the tank and prevent contamination)
  - Do not overlook the safety of the vessel in case the filter plugs. Protection may need to be provided for over pressure and vacuum hazards.

Care must be taken with preventative strategies to ensure no form of contamination develops allowing the material to become adulterated prior to the control steps. For example, in United States Pharmacopeia (USP) water systems, it is expected that the process water will meet the specification prior to the water being ozonated or heated to prevent contamination in the storage and distribution system.

Another prevention strategy is to design the system to be effectively cleaned, sanitized and drained. Examples of this strategy include:

- The selection and orientation of pumps
- Designing with expansion in mind without creating dead legs
- Not having excessive instrumentation
- Appropriately sizing and scaling the overall system; particularly tanks and other storage systems

The Design Aspects

There are six basic principles that apply to the design aspect of cleanable. These principles may be applied in greater or lesser degrees depending on the product, process and inherent risks.

1. Use of inert materials: materials must be non-reactive, non-absorptive, and compatible with the materials and the processes, including cleaning and sanitization.
2. Specification of smooth surfaces – smooth surfaces aid the removal of material and minimize biofilms. ASME BPE lists four surface designations for mechanically polished surfaces (SF0 – SF3) and three for mechanically polished and electropolished (SF4 – SF6)[1] - *Table A.*
3. Prevention of product accumulation: reduces cleaning time.

Surface Designation	Ra Max	
	µm	µin.
SF0	No finish requirement	
SF1	0.51	20
SF2	0.64	25
SF3	0.76	30
SF4	0.38	15
SF5	0.51	20
SF6	0.64	25

Table A. R_a readings for metallic product contact surfaces.

4. Specify as cleanable in place: the system utilizes flow of cleaning solutions to clean.
5. Design for easy disassembly: equipment that cannot be cleaned in place is easily removed for cleaning elsewhere.
6. Design for simplicity: simplicity of design includes reducing complexity, scale, size and all the above factors.

Cleanable

The ability to fully remove products or materials from the system is an essential requirement, not only to meet regulatory requirements, but also to minimize the impact of the residues on product functionality, color, odor and appearance. In addition, it is impossible to effectively sanitize the equipment unless all product/materials residues have been removed from the system.

The following important questions need to be asked during the design phase when utilizing the six principles that apply to the design aspect of cleanable:

- What is considered clean and how is it measured (this is of particular significance for actives or products containing active materials)?
- What chemicals will be used to clean the system - water, purified water, detergent solutions, abrasives, etc?
- How will the system be cleaned?
  - What are the flow paths?
  - Can the cleaning solution be recirculated or is it a single pass system?
  - Is the system drainable and where are drains needed?
  - Are there other flow-paths connected that will not be cleaned at the same time?

Drawing a system flow diagram and showing an overview of the required flow paths helps ensure the correct number and location of valves and instruments.

Figure 1 shows the discharge of a making system (in the upper left) sending product through a valve manifold to

Tank C (orange line). At the same time, the line from the valve manifold to Tank B (red line) is being washed to drain at the bottom outlet of Tank B. And Tank A is supplying product (blue line) to packing. During the cleaning process, it is critical to effectively separate cleaning flows from parts of the system which may still contain product.

During design, in addition to answering questions about how the system is cleaned, the layout also needs to be considered. The ease of cleaning a system is strongly impacted by the following:[1]

- Complexity – the more complex the flow path the harder it will be to clean. Simplicity of design and instrumentation can be a key factor in making the design cleanable.
- Dead legs – dead legs are sections of pipe that are not washed through in the normal cleaning flow path. Dead Legs may be an instrument tee or a piping tee that leads to another process. Since there is no flow through a dead leg, turbulence is required to clean it. The longer the dead leg or the more viscous the product to be cleaned, the greater the amount of turbulence is required to clean it.
  - ASME BPE-2012 states: "dead legs will be measured by the term L/D, where L is the leg extension from the I.D. wall normal to the flow pattern or direction, and D is the I.D. of the extension or leg of a tubing fitting or the nominal dimension of a valve or instrument. For valves, L shall be measured to the seal point of the valve."[2]
  - ASME BPE-2012 also states: "there is evidence that an L/D of 2 or less may prevent the branch from being a dead leg;" and "An L/D of 2 or less is recommended but shall not be construed to be an absolute requirement."[2]
    - > The number of recommended maximum diameters has changed over time being as high a six and dropping down to three (though the principle of clean design is to achieve zero).
    - > Since there is no flow through a dead leg, turbulence is relied upon to clean it. The longer the dead leg or the more viscous the product to be cleaned is, the more turbulence that is required to clean the dead leg.
  - For example, the dead leg in Figure 2 is the distance to the wafer in a butterfly valve from the inside wall of the main line. As an example, if the tee has an internal diameter of 1.87 inches (D), the maximum recommended distance from the inside of the main line to the sealing surface of the butterfly valve (L) is 2 × 1.87 = 3.74 inches.
  - An area that is often overlooked is the non-flow through nozzles of tanks (such as instrument nozzles). If the nozzle has a probe or dip tube extending through it, the annular space is considered the D for calculating L/D.
  - Experimental data also has indicated that the viscosity of the product to be removed is a significant factor in defining the significance of a dead leg.
  - The above recommendations are intended for products with a viscosity similar to water. Thicker products will require significantly shorter dead legs.
  - The orientation of the dead leg with respect to the flow path is critical in the overall cleanability of the dead leg.
- Tee orientation: when a tee is installed, there should be attempts to orient the tee so that the normal flow for cleaning is in one end of the tee and out the middle port. This provides higher turbulence and can reduce the time and solution required for cleaning, particularly for higher viscosity products - *Figure 3*.
- Line size expansions – Turbulent flow and wall velocity can have impacts on the ability of a system to be cleaned. Increasing the line size without a consequential increase in flow rate or velocity will result in less turbulence and less velocity. More cleaning time and cleaning solution will probably be required.
- Tanks with internal fixtures (i.e., baffles, agitators, dip tubes) – there are a variety of spray devices that can provide effective tank cleaning. Many of the older style spray balls rely on simple dissolution in excess water to clean. In these cases, the surface area

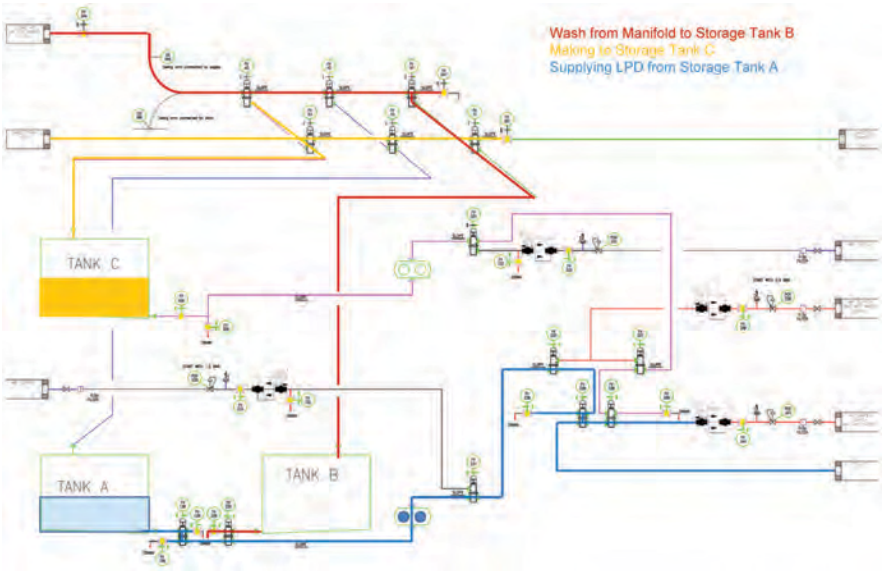

Figure 1. System flow diagram.

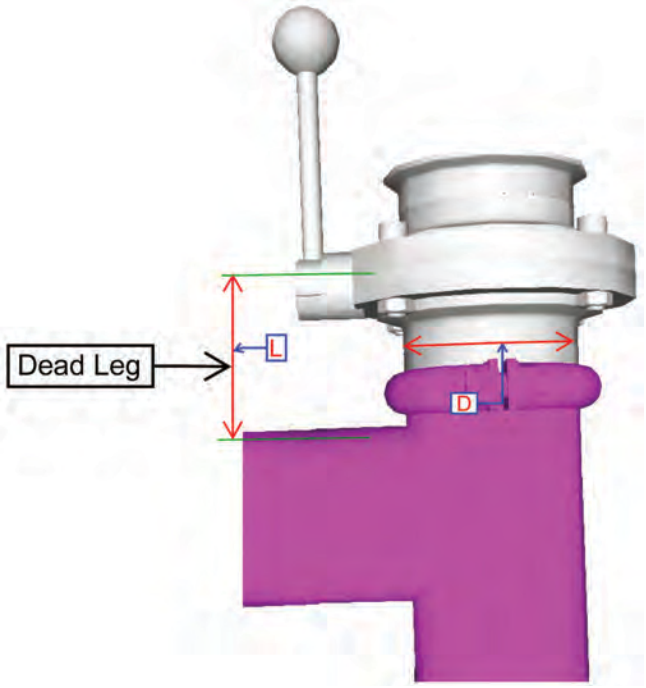

Figure 2. Dead leg example.

is not impacted by the scouring effect of the modern spray jets. The composition of the product or selection of the appropriate cleaning agents to remove the product can be the key rate determining step in the cleaning process.

- Spray devices – the effectiveness of a spray ball will depend upon factors such as:
  - How soluble the tank residue is in the cleaning solution.
    > This solubility can go back to the idle time management - if the product residue is allowed to remain in the tank, it may tend to dry out over time and may not be as soluble after one week as it was after one day.
  - The size of the tank.
  - "Shadow areas" created by internal fixtures such as baffles and dip tubes.
  - The pressure and flow rate of the cleaning solution.
    > Since solution velocity can be important, do not neglect the sizing of the supply and return (drain) lines of the cleaning solution.
  - The finish of the tank surfaces.
  - The angle of impact of the spray jet on the tank wall.

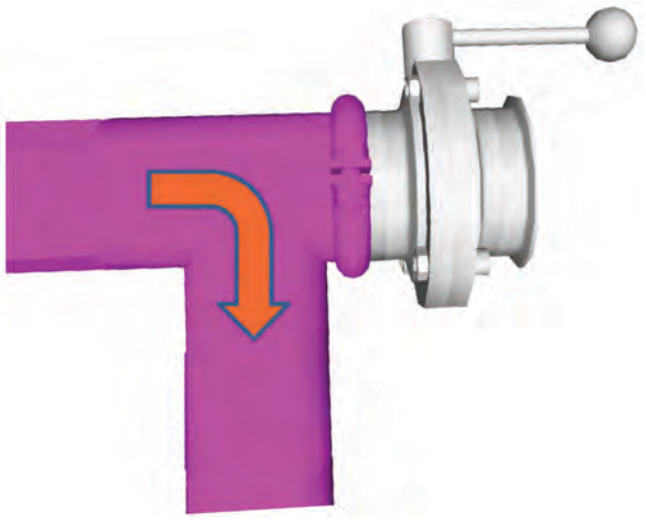

Figure 3. Preferred tee orientation for cleaning.

Additional considerations for the cleanability of tanks and associated flow paths would be:

- Pressure relief systems that need to be lifted or actuated to prevent them from becoming a dead leg or point of product accumulation.
- Contingency systems – additional pumps or flow paths installed to assure continuity of production.

Sanitizable

The ISPE Sterile Baseline® Guide defines sanitization as:

> *"That part of decontamination that reduces viable microorganisms to a defined acceptance level; normally achieved by using a chemical agent or heat to reduce microbial levels."*[3]

Moist heat is frequently used for routine sanitization – normally by hot purified water or clean steam applied continually for a minimum period proven to be effective during validation. The recommended sanitization period is usually 30 minutes. The required quality of water for the product will determine the required quality of the water and the steam used for sanitization. Moist heat is preferred over other media as it is significantly more effective than dry heat and it is easily transferred by conduction and so is capable of overcoming minor design deficiencies such as small dead legs and air pockets. This can be a significant advantage over chemical sanitization.

However, there can be some drawbacks to heat sanitization:

- Heat sanitization can impact specifications for some of the materials used in construction of the system particularly the elastomers and valve seats. This is a good example of the choice of higher initial capital cost providing a long term reduction in operating costs due to the flexibility of moist heat sanitization.
- Running 30 minutes of water to the drain though the system can be expensive; however, this can be reduced

by having a recirculation loop with a heat exchanger – though the connections to this recirculation loop need to be temporary or isolatable to assure the micro integrity is adequately addressed.
- Operator safety – water or steam leaks at these temperatures can cause serious burns.
- Environmental and building codes may limit discharge temperatures to drains.
- Steam generated in the room by the hot water or steam as it goes to the drain also may need to be addressed.

Steam is usually chosen as an option for saving water and for larger tank spaces, etc., but there are a few items to be considered before choosing that option:

- Elastomers such as Viton A will swell when exposed to steam for 30 minutes of sanitization; this is not a temperature rating issue. A consequence of this swelling is that valves may stick in the last position until the swelling goes down (the authors have observed 30 to 60 minutes). There are other grades of Viton that have better compatibility with steam, but they currently aren't readily available for many products. Other elastomers have better steam compatibility, but may not have the required process compatibility.
- Clean steam (plant steam produced using FDA approved chemicals) will require the system to be rinsed with purified water after sanitization to remove any potential contaminants.
- Steam also can contribute to wet/dry cracking, especially if there are residual chlorides from the product still in the system. This may help define the standard of cleaning required prior to sanitization.

Chemical sanitization agents, such as hypochlorite, peracetic acid, or quaternary ammonium compounds, can be used as an alternative to moist heat. In these cases; however, there are some key design parameters which must be considered:

- The materials of construction of the system must be fully compatible with the sanitizing agent.
- There must be a means of assuring the concentration of the sanitization agent remains at or above the specified level.
- There can be no air bubbles or areas of the pipework which do not come into contact with the sanitizer; therefore, the location of vents and drains take on added significance.
- Tanks need to be filled with sanitizer solution or the spray device must assure complete coverage.
- The system will require that rinsing and an effluent disposal system are included in the design.

Drainable

Systems have to be designed to be fully drained if they are to be cleaned and sanitized effectively. Process lines that are normally drained of product, cleaning solutions, or sanitization solutions during part of the cleaning and sanitization process should have a minimum 1% slope while a 2% slope is preferred. Valves need to be properly oriented to fully drain. For example, diaphragm valves usually need to be installed with the stem rolled to an angle when installed in horizontal pipes. Instrument probes and sidewall penetrations also should be sloped for drainage unless the instruments require horizontal mounting.[4]

BioPharm elbows and tees are available with 88°, 90°, and 92° angles to help achieve these slopes (2° is actually greater than 2% and this meets the requirements). Sloping, together with the provision of suitably designed and located drain valves, will assure the system is free draining of normal viscosity products. Highly viscous products may need heat traced pipework or increased slope to assure drainage.

Drainability is important as it impacts idle time management. If product/process lines cannot be completely drained after cleaning, there are a number of options which can be used to reduce the risks of microbial growth.

1. Dismantling the system after cleaning to assure all residues can be effectively removed and drained. The system will need to be sanitized prior to reuse.
2. Purging the system with compressed gases, the gas itself must be proven not to be a contamination source.
3. Pigging the system. Pigging is the propulsion of a mobile plug through a line for a specific purpose. In this case, the purpose is clearing the bulk of the product from the lines – pushing the product either to a filler or back to a tank.
4. Flush the residual condensate or water with products.

This last option does come with some additional risks and validation requirements. The diluted product is a major contamination risk, and the system must be flushed immediately after sanitization and the residual product or material must be disposed of immediately and not recycled. This whole process would need careful validation to assure there was no adulteration of the product. There should not be additional water in the system that has not been removed prior to sanitization or use.

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About the Authors

Neil Lewis graduated with a BSc in microbiology and parasitology in 1979. He spent the next 12 years working for Max Factor and Revlon, initially as the site microbiologist at the international manufacturing site in the UK and ultimately as the special projects manager for the European Revlon group. He transferred to The Procter and Gamble Company (P&G) with the Max Factor acquisition in 1991 and assumed Quality Assurance (QA) responsibilities for Health and Beauty Care operations for Western Europe. This was followed by an assignment at one of P&G's Health and Beauty Care primary manufacturing sites. In 1999, he transferred to the Household Care division to develop a global microbiological control program for the Household Care operations. The successful completion of this program in 2010, led to the request to reapply the program design and operations to the other P&G business units. Lewis's current role encompasses all the technical aspects of the microbiological control programs in all P&G global manufacturing sites, including clean equipment and facility design, development of novel cleaning and sanitization processes, design and implementation of rapid testing methodologies, and the development of microbiological risk assessment programs. He is a member of the Online Water Bioburden Analyzer (OWBA). He can be contacted by email: Lewis.NJ@pg.com.

Steve Shank graduated with a BS in chemical engineering in 1979 followed by an MBA with emphasis on production and operations in 1981 He spent the next eight years working in production in Houston; initially as the process department supervisor at Clorox and ultimately as the plant manager for South Coast Terminals. He moved to Cincinnati and started working as a process engineer. For the last 14 years, Shank has been working for Process Plus, a full-service engineering and design firm focused on the pharmaceutical, chemical and food and beverage industries. Utilizing his expertise in clean design, for the past six years, he has been providing specialized process engineering services to regulated industries in North America, Europe and Asia. Shank is a licensed Professional Engineer in the state of Ohio and a member of ISPE. He can be reached by email: sshank@processplus.com.

On-Line TOC Monitoring in GMP Parts Washers

by Marcel Dion, Olivier Van Houtte, and George Verghese

This article presents a TOC monitoring system integrated into a parts washer and discusses how it can increase productivity, help meet PAT and QbD goals, and provide ongoing assurance over the life cycle of the process.

Total Organic Carbon (TOC) analysis is one of the most common analytical methods used for cleaning validation in the pharmaceutical industry. This non-specific method is typically used to detect the presence of organic residues on cleaned product contact surfaces. In conventional automated cleaning systems, such as Clean Out-of-Place (COP) parts washers, a sample of the final rinse water is analyzed for TOC off-line. This approach requires that a sample be manually taken from the washer and transferred to a laboratory for TOC analysis. A new technology is now available that allows this analysis to be performed by the washer itself.

The benefits of using such a system range from allowing cycle time optimization to reducing the risk of contaminating rinse water samples. Cross contamination is a critical concern in pharmaceutical research and production environments and the application described below explains how the chosen approach can help reduce this risk by providing process trending data and assuring robustness.

With the recent regulatory developments in the pharmaceutical industry driven by ICH guidelines Q8, Q9, and Q10, and the new U.S. FDA process validation guidance document released in January 2011, the emphasis on continued process verification has increased. This article describes a TOC monitoring system integrated into a parts washer and discusses how it can increase productivity, help meet Process Analytical Technology (PAT) and Quality by Design (QbD) goals, and provide ongoing assurance over the life cycle of the process.

Application Description

GMP Parts Washer Application

Pharmaceutical grade washers are generally required for critical cleaning and drying applications in pharmaceutical and biopharmaceutical manufacturing facilities. Typical applications include manufacturing of injectable and other oral or solid dosage drugs that are regulated by Good Manufacturing Practices (GMPs). These washers are typically used to clean and dry a wide range of components, such as laboratory glassware, liquid and powder filling line components, stainless steel mixing drums, fermentation containers, freeze dryer trays, tablet punches and dies, vials and ampules, filter housings and change parts for blistering, packaging and counting equipment, just to name a few. The complexity may vary from very simple small parts to highly complex large parts and systems that may require sophisticated spray devices.

FDA 21CFR Part 211 (§ 211.65) provides that, "equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other stated established requirements."

This is why pharmaceutical grade washers are generally only required for applications where the components listed above are in contact with the product(s) being manufactured. Otherwise, regular glassware washers can generally be used. Although the installation and operation of most standard laboratory washers can be qualified, these lower cost washers are not provided with the documentation and sanitary design that is normally required for GMP applications.

COP washing is only suitable for applications where the parts can be removed from the manufacturing process and transferred to the washing area. When the items to be cleaned are too large, too heavy, or cannot be taken out of the manufacturing process, Clean-In-Place (CIP) systems are the suitable choice. The online TOC monitoring system described below also can be implemented in CIP systems.

TOC Monitoring Application

The soils involved in these types of GMP parts washing applications vary widely. While some applications may involve easy-to-clean, water soluble soils, others may involve cleaning of tenacious residues that may be highly toxic and may call for stringent acceptance criteria and close monitoring. This is why monitoring of Critical Quality Attributes (CQAs) during the cleaning process of these soils is valuable. A TOC analyzer that is integrated into the washing systems allows for monitoring even more closely the CQAs.

In parts washers, cleaning parameters, such as temperature, mechanical action (pressure, force), detergent concentration, coverage, and cleaning time are measureable and have a great influence on the cleaning performance. A good understanding of the relationship between these parameters, cleaning process objectives and the critical process quality attributes is important. The process must be designed to remove soil residues adhered to the surfaces as well as to remove detergent residues and other trace contaminants from the rinse water. In order to ensure adequate removal of these residues, both surface swabbing as well as rinse water analysis are commonly performed. The analytical methods used for rinse water analysis are typically the standard non-specific methods-conductivity and TOC, or in some cases, a specific method such as HPLC.

Conductivity typically measures inorganic conductive species in the rinse water. TOC measures organic compounds that are typically associated with the soil. So these two analytical methods are independent and complement each other. Therefore, the combination of online TOC and online conductivity measurements provides a more complete means for near real-time verification of cleaning cycle performance, and for using statistical process control methodologies for ongoing analysis of the consistency of critical quality attributes for the cleaning process.[1]

It must be noted that each user needs to define what level of residue is permissible on a cleaned process part that is subsequently introduced into a drug manufacturing process. This residue level is determined based on a risk assessment and on an evaluation of the influence of that residue on the product quality and patient health.[2] The sampling of residues from parts typically involve both rinse and swab methods. The on-line TOC monitoring system discussed in the article is limited to rinse solutions and sampling. It is not an alternative to the manual swab methods that are typically used during cleaning process qualification.

Regulatory Drivers and Trends

In recent years, pharmaceutical companies' practices have been strongly influenced by numerous guidelines and standards which have set the bar higher in terms of life cycle process validation. These standards call for "collection and evaluation" of data throughout the life cycle of the process. In January 2011, the FDA released the guidance document entitled, "Process Validation: General Principles and Practices" replacing the earlier guidance issued in May 1987. The new guidance defines process validation as, "*The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.*" It describes process validation activities in three stages, all of which involve collecting, analyzing and evaluating process-related data.

Stage 1 – Process Design

The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes.[3] The process design phase allows understanding critical and non-critical parameters and attributes which will determine the actions to be taken in the next stages. During this phase, several cleaning runs may need to be completed to define the parameters that will produce acceptable cleaning results. The ability to quickly obtain results from TOC analysis of final rinse water samples can help reduce the overall time required for this phase.

Stage 2 – Process Qualification

During the Process Qualification (PQ) stage of process validation, the process design is evaluated to determine if it is capable of reproducible commercial manufacture. This stage has two elements: design of the facility and qualification of the equipment and utilities, and Process Performance Qualification (PPQ). This stage requires writing and executing protocols that specify the conditions, controls, testing, and expected outcomes. It involves a high level of sampling, testing, and scrutinizing of the process performance at commercial scale.[4]

Stage 3 – Continued Process Verification

The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal. Adherence to the cGMP requirements, specifically, the collection and evaluation of information and data about the performance of the process, will allow detection of undesired process variability. Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control (§ 211.180(e)).[5]

The ICH guidance Q8 defines "*continuous* process verification" as "an alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated."[6] It is a science-and risk-based real-time approach to verify and demonstrate that a process that operates within the predefined specified parameters consistently produces material which meets all its critical quality attributes and control strategy requirements. Extensive in-line or at-line controls and monitoring of process performance and product quality is required in a timely manner to enable continuous process verification. This should include verification of attributes, parameters and endpoints, and assessment of CQA and Critical Process Parameters (CPP) trends. The EMA's March 2012 Draft Guideline on Process Validation allows for a hybrid approach where this alternative continuous verification approach may be used only in some of the steps in a multi step process.[7]

No matter which approach is followed, it is clear that the regulatory trends and expectations point to the need for significant data collection and evaluation, and for establishing consistency, maintaining a state of control, and adopting science-and risk-based decision making. The traditional three-batch checklist approach to validation is no longer supported by regulators for producing drug products that can be safe for use and ultimately commercialized.

System Description

The complete system includes a TOC sensor/analyzer that is fully integrated into a pharmaceutical grade parts washer. The design of parts washers varies slightly from one supplier to another; however, the concept is basically the same for all manufacturers. The heart of all parts washers is the wash chamber in which parts (components or items) to be cleaned are processed. The chamber is typically fitted with spray arms that provide complete cleaning solution coverage on all the external surfaces. The parts to be cleaned are positioned in baskets (or on racks) that are equipped with various spindles, nozzles and connectors to ensure all the internal surfaces of the items also get complete coverage. Because coverage is one of the most critical parameters that affect cleaning, monitor-

ing of the spray arm action is recommended.

The bottom of the wash chamber is generally referred to as the sump. The sump is normally equipped with a sampling port, allowing users to manually take water samples for off-line TOC analysis. This is also where heating elements (steam or electric coils) are located. The heating system ensures that the appropriate temperature is maintained during the critical steps of the cycle. The spray systems and baskets/racks are linked to the piping system which usually includes a recirculation pump and a number of sanitary valves.

A typical cleaning cycle is comprised of various phases, each phase including different steps. Cycles typically start with a "pre-wash" phase to reduce the amount of soil on the load items prior to proceeding with the "wash" phase. Fresh water is introduced in the sump until detected by a level sensor. The circulation pump then starts and the heating system is energized, if applicable. Once the time programmed for this pre-wash phase has elapsed, the water is drained. These steps are repeated for the "wash" phase that follows. The main difference with the wash phase is that a detergent, or in some cases more than one detergent, is injected in the sump at the beginning of this phase. A common practice in the industry is to monitor and control this injection or dosing using a conductivity system. This process provides a high level of assurance that the right amount of detergent has been added. Some cycles may utilize more than one wash phase such as an alkaline wash followed by an acid wash. The wash phase is followed by the "rinse" phase(s). In most cases, two rinse phases are required to remove the majority of chemical residues. Each of those rinses utilizes fresh water. The last phase of the cleaning process, called "final rinse," uses higher quality water, in many cases, Water For Injection (WFI).

Another common practice in the industry is to monitor the conductivity of the final rinse water on-line. A measurement of the conductivity is performed immediately after the rinse is completed. If the reading is higher than the set point, the final rinse is repeated. The final rinse phase is repeated until the reading is below the set point, or until the maximum number of rinses has been reached, in which case an alarm will be generated. Until recently, conductivity was the only on-line method that could be reliably used to monitor the quality of the final rinse water. Now the TOC technology has become robust and affordable enough to be integrated into washing systems.

One of the ways this technology is incorporated into a standard washer is by using a multi-parameter analyzer/transmitter and TOC sensor, which are integrated into the piping system, with the analyzer/transmitter connected to the washer Programmable Logic Controller (PLC).

The TOC sensor described in this article uses ultraviolet oxidation with differential conductivity as the method to determine TOC concentrations in the final rinse water sample. This type of analyzers requires that the sampled water be within a specified conductivity range to prevent the TOC calculation from being skewed.

When using a TOC sensor that uses differential conductivity as the detector for TOC measurement, the conductivity of the rinse water is first measured after the final rinse using a conductivity probe that is located in the sump of the washer and interfaced with a conductivity analyzer. As explained above, rinses are automatically repeated until the conductivity is lower than the set point, and until it has reached the level that is within the operating range of the TOC analyzer. A controlled amount of final rinse water is then directed to the TOC sensor assembly through an isolation valve - *Figure 1.*

This design maximizes exposure to the 185 nanometer

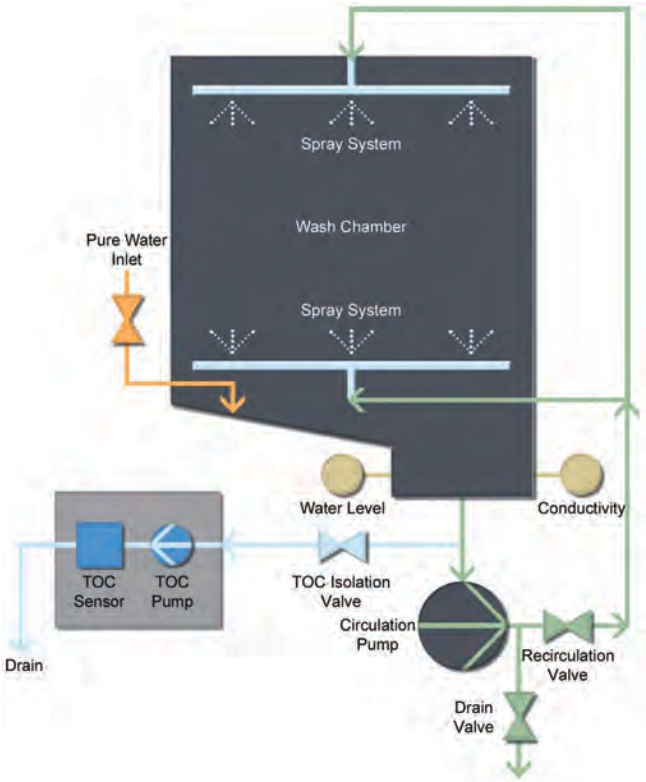

Figure 1. Washer chamber and TOC system layout.

UV light, while minimizing measurement response time and providing complete oxidation. Once the sampling time is elapsed, the multi-parameter analyzer transmits the TOC value to the washer PLC control system. If the value is higher than the TOC set point for that particular cycle, the cycle stops and an alarm message is generated. After acknowledging the alarm, the operator can either accept the value or abort the cycle. If the value is accepted, the cycle resumes to the next phase; the final rinse water is drained and the drying phase starts. Alternatively, the control can be programmed to repeat the rinse phase until the set point has been reached, or until a maximum number of rinses have been completed. Failure to achieve these programmed parameters can trigger an alarm to indicate that the process was not successful.

Functional Description

The washer first proceeds through its pre-programmed pre-wash, wash, and rinse phases. After the final rinse phase, the conductivity of the water is measured prior to draining the sump (the conductivity range is typically 0.0 - 2.0 µS/cm). The final rinse sequence is repeated until the conductivity set point is reached. For the system described in this article the conductivity is required to be < 2 µS/cm before the TOC system can be used. After this step, the TOC monitoring system is turned on and TOC sampling of the final rinse water is

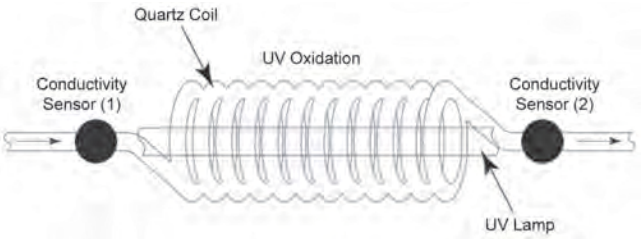

Figure 2. Conductivity measurement before and after oxidation (schematic courtesy of Mettler-Toledo Inc.).

performed. The rinse water is automatically pumped into the TOC sensor as seen in Figure 3.

The duration of the sampling sequence may vary and can potentially be optimized based on the system configura-

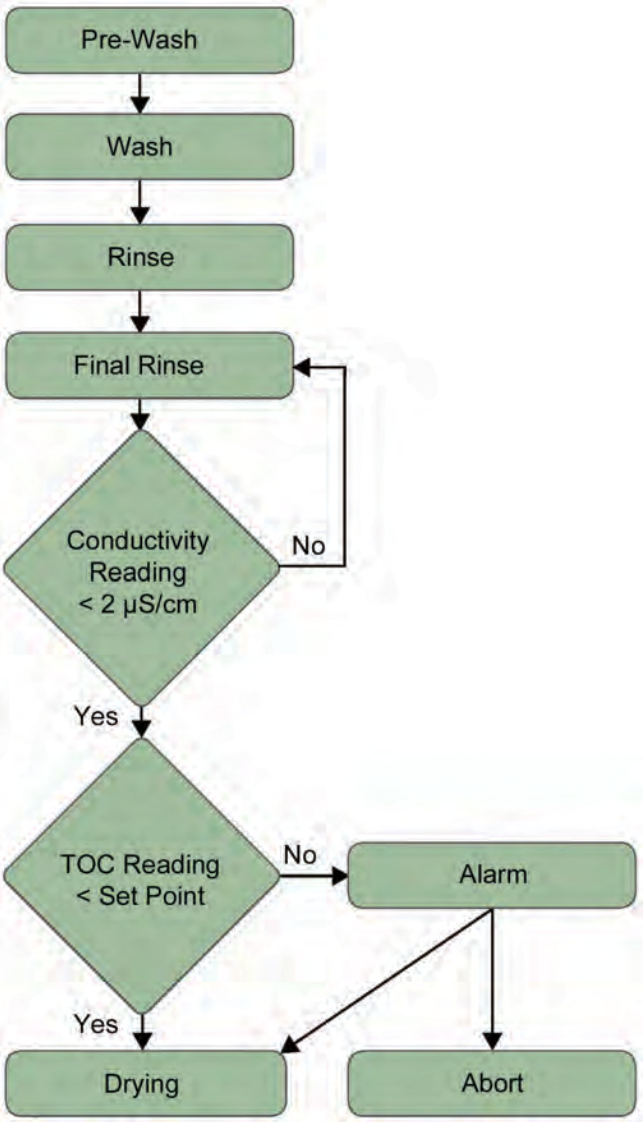

Figure 3. On-line TOC functional description.

tion, design, and flow parameters. The sampling time for the system described in this article is set between six and 12 minutes. Testing data illustrated in Figure 4 demonstrates that approximately five minutes are required for the data to stabilize. The TOC measurement range for this system is limited to 1 to 1000 ppbC (µgC/L) and the sensor has a Limit of Detection (LOD) of 0.025 ppbC. Although the acceptable TOC limits vary depending on the application as mentioned earlier, this range is well within the typical analytical range for the use of TOC for cleaning validation.

Data collected from washers with this online TOC monitoring system that have been used for almost three years in a large biopharmaceutical facility shows that stable operation and results can be obtained. Cycles for these washers include two wash phases, one using a potassium hydroxide based detergent at 4% concentration and one using a phosphoric and citric acid based detergent at 2% concentration. Stabilization time on these washers was set to eight minutes to ensure constant results. TOC values measured after three recirculated rinses with Reverse Osmosis (RO) water and two single-pass rinses with Water For Injection (WFI) varied between 50 and 150 ppbC.

At another biopharmaceutical facility, the TOC monitoring system installed on one of the washers was very useful for troubleshooting problems during cycle development. Although their baseline TOC readings were in the range of 30 to 80 ppb in the rinse water, some of the parts were retaining small quantities of water during the rinse cycle. This led to spikes in their TOC values ranging from 700 to 1000 ppb, which was above their acceptance criteria of 500 ppb. The use of the on-line TOC monitoring system helped address these liquid hold up issues in a timely and efficient manner. The on-line TOC values were verified using a laboratory based TOC instrument during the qualification stage. The end user also performed swabbing for TOC on select product contact parts during the validation stage to support their cleaning validation. The TOC monitoring system has been in use now for over a year at this particular location.

Advantages

The integration of a TOC analyzer to a COP (or CIP) washing system appears to offer several benefits for users and the validation team.

1. **Shorter cycle development time due to immediate feedback.** The on-line monitoring system provides TOC results within minutes after sampling of the final rinse water, and before the cycle is completed. With off-line operation, the manually taken sample has to be sent to the testing laboratory, which can either be located at the site itself, or in some cases at another site, or in another building. The time it takes to obtain the results back from the laboratory can vary largely from one facility to another. It can be a few hours, or it can be several days. The ability to obtain almost immediate results was found to be particularly appreciated by the user mentioned above, especially as they went through the cleaning validation process. During this key step, critical cycle parameters are defined and optimized, requiring that several loads be run per day. By knowing the TOC analysis results immediately after cycles are completed, adjustments to the parameters can be made quickly, thus considerably reducing the overall time to complete the cycle development process.
2. **Reduced labor.** Since the sampling of the final rinse water is done automatically by the system, there is no need for an operator to access a sampling port and manually fill a sampling bottle or to walk over to the laboratory, or send the sample by courier to another site. The savings here can represent several minutes of valuable man power. Additionally, the operator does not need to stand by the washer and wait until the appropriate time during the cycle to take the sample.
3. **Reduced risk of contaminating rinse water samples.** By nature, manually taking samples increases the risk of introducing contamination of those samples. The containers themselves can be a source of contamination; the operator also can make manipulation errors. Contamination can occur during transportation of the samples, or during the analysis at the laboratory. An on-line, automated system basically eliminates these potential sources of contamination.
4. **Increased assurance of successful cleaning process.** TOC analysis is typically performed to add another layer of assurance that the cleaning process has been successfully completed. Until recently, COP washers were only equipped with conductivity monitoring systems. While conductivity can provide a good indication of residual chemicals, such as alkaline or acidic detergents, it typically cannot be used to detect the presence of the soil itself. When the soils are organic based, TOC measurements provide a more complete analysis of the residues found in the rinse water. This is why many facilities use TOC in addition to conductivity as an analytical method for cleaning validation. Because of the labor involved in the manual process; however, many users do not take samples for each and every washing cycle. The on-line monitoring system can be programmed to take a sample for each and every load, thus assuring better process trending, robustness and continued process verification.
5. **Safety.** Final rinse water, which is often Water For Injection (WFI), is typically very hot. The final rinse is generally programmed to be performed with hot water to help with reducing drying time. By eliminating the manual sampling process, users are less exposed to hot water and surfaces.
6. **Reduced equipment downtime.** Since results from the TOC analysis are readily available, components can be released more quickly thus reducing manufacturing equipment downtime.
7. **Reduction of water consumption and cycle time.** Since TOC analysis can be automatically performed for all cycles, there is no need to develop an "overkill" cycle with excessive number of rinses, just to be on the safe side. A reduction in the number of rinses results in shorter cycle time, lower operation costs, and increased productivity.

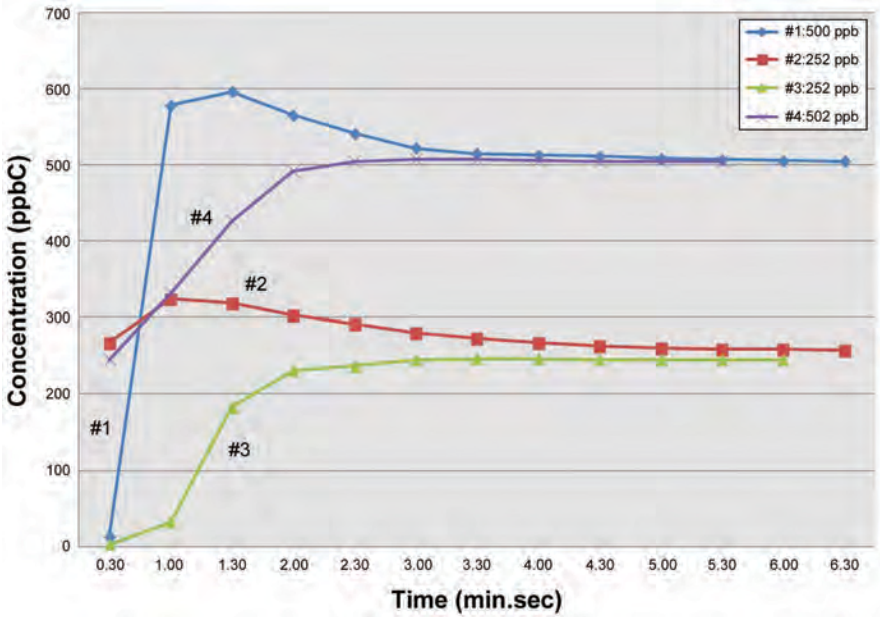

Figure 4. Concentration and time values for TOC calibration.

Disadvantages

1. **Longer wash cycle.** As described above, the TOC analyzer requires a few minutes for the data to stabilize. This time is actually added to the total time it takes to complete the wash cycle. This disadvantage is somewhat offset by the fact that some additional time

is also required if the sampling is done manually. In this case, an operator has to either be on standby waiting for the appropriate time during the cycle to manually take the sample, or the washer has to be programmed to stop at the right time during the cycle until the operator has taken the sample and resumed the cycle.

2. **Higher acquisition cost.** Although the cost of the TOC technology has significantly decreased during the past few years, its integration in a washing system remains a non-negligible capital investment and it does not necessarily eliminate the need for acquiring another off-line TOC analyzer for the laboratory.
3. **Higher maintenance cost.** The robustness of the TOC technology also has increased over the years. However, an on-line monitoring system does require regular calibration. The IQ/OQ process for the washer may be extended; the need for specialized maintenance resources may be required.

Conclusion

The cleaning of pharmaceutical manufacturing equipment systems by automated means has long provided superior reliability and consistency as compared to manual cleaning operations, which are subject to human error. Through the introduction of more reliable and affordable sensors, including advances in online TOC technology, the cleaning process can be very effectively controlled and monitored by removing variability inherent to manual collection and analysis of cleaning verification and validation samples.

The on-line TOC monitoring system measures a critical quality attribute, allowing process trending and analysis ensuring robustness. All these benefits result in reduced cycle development time and risks of contamination, lower labor requirements, increased safety and assurance of successful cleaning process, reduced equipment downtime, optimized cycle time, and lower rinse water consumption.

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About the Authors

Marcel Dion is Director of Marketing for Washing and Steam Sterilization Systems in the Life Sciences Division of STERIS Corporation. Dion holds a diploma in instrumentation and control from Levis-Lauzon CEGEP in Quebec, Canada. He was involved in designing and manufacturing washing systems for the life sciences industry during the first 20 years of his career. For the past 13 years, he has been responsible for developing and bringing to the market innovative and efficient cleaning and steam sterilization systems for critical parts/components that are involved in the drug manufacturing process. Marcel has been a member of ISPE, PDA, LAMA and AALAS organizations for several years. He can be contacted by email: marcel_dion@steris.com.

STERIS, 490, Armand-Paris, Quebec, Qc, Canada, G1C8A3.

Olivier Van Houtte is Associate Product Manager in the Life Sciences Division of STERIS Corporation. Van Houtte holds a bachelor's degree in business-marketing from Quebec University in Quebec City, Canada. He is responsible for managing a broad product portfolio intended for the pharmaceutical and research industries. He is a member of the ISPE, PDA, LAMA and AALAS organizations. He can be reached by email: olivier_vanhoutte@steris.com.

STERIS, 490, Armand-Paris, Quebec, Qc, Canada, G1C8A3.

George Verghese is director of technical services in the Life Sciences Division of STERIS Corporation. He manages the technical services group for formulated chemistries and oversees the Process and Cleaner Evaluation (PACE) Laboratory. Prior to STERIS, he held engineering positions at Bristol-Myers Squibb and Calgon Vestal, a subsidiary of Merck & Co. Verghese has written numerous articles on topics related to contamination control and is a frequent speaker at industry conferences. He holds a master's degree in chemical engineering and is a member of the ISPE, PDA, and ASTM. He can be reached by email: george_verghese@steris.com.

STERIS, 7501 Page Ave., St. Louis, Missouri 63133, USA.

New Quality Culture Drives the Comeback of Pharmaceutical Engineering

Quality in the pharmaceutical industry is facing a restructuring in quality management. The manufacturing goal of producing consistent, high quality products with minimal regulatory oversight is revealing a new path. The FDA and CDER are in the process of restructuring with the proposed Office of Pharmaceutical Quality and the European Medicines Agency (EMA) continues to update chapters and annexes of the EC GMP Guide in order to prevent cross contamination or ensure end to end supply chain integrity. All of these changes will have an impact on manufacturing processes, material flow, and factory layouts as well as on quality systems design and quality risk management.

Furthermore, the issue of drug shortages leads to an alignment between the FDA and EMA requiring consolidated industry feedback about root causes, mitigation prevention, and regulatory interaction.

"The impact on quality systems and on quality culture will be significant, according to Dr. Thomas Zimmer, ISPE's VP of ISPE European Operations, it is up to industry stakeholders to prepare, educate, and discuss the new conceptual framework of manufacturing."

Adopting a Quality Culture philosophy involves the entire pharmaceutical network. There must be a total commitment to invest and embrace the change toward the desired state of continual quality. Mutual learning, sharing knowledge, and analyzing "root causes" are essential parts of adopting a culture of quality.

ISPE acknowledges their part in quality culture by bringing together industry professionals to share recent knowledge and discuss the implementation and importance of proactive quality management. ISPE's new Europe Annual Conference will take place on 28-30 April, 2014 addressing this modernization of quality manufacturing. The Sheraton Frankfurt Airport Hotel and Conference Centre in Frankfurt, Germany will host the inaugural conference themed "Driving Effectiveness in Pharmaceutical Operations with the new Quality Culture." Pharmaceutical, regulatory, and technology experts from around the world will explore current operational challenges and quality systems effectiveness, including current regulatory trends. Industry opportunities, such as Quality by Design (QbD), science-and risk-based approaches, and continuous manufacturing also will be discussed.

According to Zimmer, "Our goal is to provide an annual event that meets an international need to discuss, collaborate, and align industry perspectives on key pharmaceutical manufacturing topics. ISPE created this conference to support European stakeholders with their efforts to develop and apply the latest technologies in manufacturing high quality pharmaceuticals."

The 2014 Europe Conference will include an executive session, plenary session, and multiple focus tracks to meet various educational needs.

Executive Forum

The Executive Forum is intended for pharmaceutical executives, senior experts, and future decision makers from all functions in pharmaceutical operations, including development, regulatory affairs, quality, production, engineering/investment management and supply chain management. Dr. Zimmer will be joined by top industry experts to discuss the future with a pharmaceutical quality culture and the essential key factors necessary to achieve successful pharmaceutical manufacturing from development to distribution.

Executive Focus Sessions

- *Falsified Medicines Directive Implementation, Delegated Acts and Mass Serialisation*
  Dr Reinhard Hoferichter, Sanofi and Head of SECURPHARM will focus on preparedness and implementation of systems and processes.
- *The Big Challenge for Pharmaceutical Operations in Europe: Managing Compliance and Quality Under New Requirements and the Perceived Trade-off to Lean, Agile and Flexible Production*
  Dr Martin Lösch, Director and Paul Rutten, Principal at McKinsey & Co, Stuttgart & Frankfurt, Germany will present an interactive session focusing on the perceived trade-off between fulfilling GMP compliance and lean production based on benchmark studies undertaken by McKinsey and Co.
- *Drug Shortages – a Multi-layered Challenge Across the Whole Supply Chain*
  Input and updates from industry experts and agencies will reflect on the current drug shortages initiatives. Discussions will incorporate FDA guidance, the EMA reflection paper, the ISPE industry survey, and the latest updates on the industry-regulator dialogue on preventative concepts and best practice examples to avoid drug shortages. Dialogue will also focus on the robustness of the installed pharmaceutical quality systems, the relevance of quality culture and behaviors within corporations.

"Three tracks were developed to address the new quality culture in a way that will facilitate a closer working relationship between engineers, QA personnel, and regulators," according to Jean-Francois Duliere, Pharmaceutical Process Technologist, Technip Life Sciences, France and

Continues on page 90.

ISPE Europe Annual Conference

28-30 April, 2014 - Frankfurt, Germany

Driving Effectiveness in Pharmaceutical Operations within the New Quality Culture

As part of the global ISPE perspective, the first ISPE Europe Annual Conference will provide an overview of regulatory trends in Europe and in the rest of the world, and will connect the evolution of the pharmaceutical industry with regulatory market and technological developments.

This inaugural Annual Conference in Europe will bring together high-level top executives and pharmaceutical, regulatory and technology experts from around the world to contribute to the creation of a new pharmaceutical paradigm.

Chaired by

Dr Gabriele Wanninger, from the Bavarian Inspectorate

Jean-François Duliere, Pharmaceutical Process Technologist, Technip Life Sciences

Thomas Zimmer, PhD, VP Technical Operations, EuropeInternational Society for Pharmaceutical Engineering – ISPE (Executive Forum)

The Conference will feature:

- An **Executive Forum** to discuss the implementation of the Falsified Medicines Directive, especially with respect to the status of the Delegated Acts of the European Commission and to Mass Serialization. As a second topic, a representative from McKinsey will conduct an interactive session on current challenges for technical operations. Finally, there will be an update on Drug Shortages.
- **Three tracks** with panels of international, senior experts, industry executives and regulatory professionals:
  - Track 1: QbD – Reality Today? Implementation and Beyond
  - Track 2: Quality Risk Management (QRM)
  - Track 3: Pharmaceutical Facilities of the Future
- Educational sessions
- Interactive demonstration workshops
- Practical case studies
- Q&A sessions

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New Quality Culture...

Continued.

Programme Committee Chair, "delegates will be able to openly discuss current technical and regulatory issues in a friendly safe environment."

Plenary Session: Defining the New Quality Culture

Implementing a solid quality culture in pharmaceuticals will have lasting implications worldwide. Patients and prescribers will be secure in their expectation of steady supplies of safe, affordable, and effective medicines. Businesses will evolve into proactive entities, preventing cost draining recalls, process reworks, and manufacturing interruptions. Pressures in the pharmaceutical industry are not specific to one sector, our entire network is under pressure in a reactive state. The solution is big and encompassing. The future is in a preemptive philosophy. A new culture of quality within the pharmaceutical industry will address the root causes and divergent patterns, so every industry sector will begin to "do things right the first time." The new quality culture moves away from the system of fixing problems and toward a system of preventing them.

ISPE has filled the Plenary Session with speakers from all aspects of quality culture. Day 2 of the conference is chaired by Jean-François Duliere (France) and Dr. Gabriele Wanninger (Germany) and includes four keynote presentations.

- Regulatory Review
- Customer View: Future Challenges in Biopharma – Prof. Dr. Wolfram Carius, Sanofi Frankfurt
- Industry View – John Pinion, Roche
- Joe DeFeo, Juran Institute

Conference Program

Jean-François Duliere, Pharmaceutical Process Technologist, Technip Life Sciences, France will chair the Programme Committee. The components of the conference program consist of three educational tracks including international senior expert panels, interactive demonstration workshops, practical case studies, and Q&A sessions for a deeper understanding of topics.

Track One: QbD – Reality Today? Implementation and Beyond

Track One was developed by key industry and regulatory experts combining practical examples, best practices, regulatory perspectives, and the latest applicable scientific information. The presentations will focus on the most up-to-date and existing global Quality by Design (QbD) practices and will benefit production managers and engineers who are responsible for implementing production of products developed under QbD. Others who will benefit from these presentations include pharmaceutical development experts, regulators, and all professionals involved in the quality of manufacturing, such as management, QA, operations, QC, and quality systems. The presenters hope attendees will share their current information and expert knowledge, as well as learn new specifics related to QbD. Key points of Track One:

- Implementing QbD in manufacturing operations
- Approaching QbD changes for successful submissions
- Applicability and benefits of QbD concepts

At the conclusion of Track One, participants should have a better perspective regarding QbD's involvement with industry and regulatory processes.

Track Two: Quality Risk Management (QRM)

Track Two will concentrate on the impact of QRM in pharmaceutical manufacturing and distribution. This track was developed for regulators, QA/QC, and production/distribution personnel wishing to learn practical methods for analyzing, evaluating, and preventing risks in day-to-day QRM which would distinctly impact GMP compliance. Key Points of Track Two:

- Impact from regulatory point-of-view
- Current QRM impacts
- Diverse practices of QRM

On completion of Track Two, participants will have gained new perspectives pertaining to the applicability of QRM as a quality tool and its current usages industry-wide.

Track Three: Pharmaceutical Facilities of the Future

As pharmaceutical companies face several challenges on revenue, patent expiries, regulatory requirements and insufficient effectiveness, there is a need to re-think the facilities of the future. New technologies, regulatory changes, and international cooperation enables innovative solutions and more effective operations. Many companies are working on concepts for their future facilities and others have recent experiences they are willing to share. Track Three brings together pharmaceutical companies, suppliers and regulators that point towards solutions for both new and existing facilities to achieve higher efficiency and cost-effective compliance solutions. This track was developed for professionals involved in manufacturing, quality management, development and technology transfer as well as suppliers and regulators with interest in new solutions and experiences.

This program combines new concepts and solutions from an experienced equipment vendor with practical knowledge of proactive changes manufacturers are making to prepare for

Continues on page 100.

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Health and Human Services Releases its Semiannual Regulatory Agenda

The following is a brief summary of the Regulatory Agenda released January 7, 2014. The agenda is a result of the Regulatory Flexibility Act of 1980 and requires departments, such as Health and Human Services (HHS), to issue an inventory of rulemaking actions providing the public with a summary of future regulatory actions. The purpose of this information is to assist the public with its participation in a department's regulatory activities. The HHS rulemaking abstracts included in this semi-annual agenda of the Federal Register only cover, as required, those prospective HHS rules expected to have a "significant economic impact on a substantial number of small entities."[1] Outlined below are the rulemakings pertaining to the pharmaceutical industry under HHS.

Pre-Rule Stage

Prescription Drug Marketing Act of 1987; Prescription Drug Amendments of 1992; Policies, Requirements, and Administrative Procedures (Section 610 Review)

RIN: 0910-AF14 **Priority:** Other Significant
Regulatory Flexibility Analysis Required: Yes
Legal Deadline: None
Timeline:

- Begin Review of Current Regulation 11/24/2008
- End Review of Current Regulation 11/00/2013

Summary: This is a FDA review of regulations under the Prescription Drug Marketing Act. Determinations will be made to whether regulations should be changed or rescinded to minimize impact on smaller entities. The FDA will consider continued need, public input, regulatory complexity, federal conflicts, and recent technological and economic changes that impact current regulations.
Contact: Howard Muller, Office of Regulatory Policy, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research
Email: pdma610(c)review@fda.hhs.gov

Proposed Rules

Over-the-Counter (OTC) Drug Review--Cough/Cold (Antihistamine) Products

RIN: 0910-AF31 **Priority:** Substantive, Non-significant
Regulatory Flexibility Analysis Required: Yes
Legal Deadline: None
Timeline:

- Reopening of Administrative Record 08/25/2000
- Comment Period End 11/24/2000
- NPRM (Amendment) (Common Cold) 11/00/2013

Summary: This proposed rule is a collaboration under the U.S.-Canada Regulatory Cooperation Council to add the common cold indication to certain Over-The-Counter (OTC) antihistamine active ingredients. The goal is to reduce differences and determine the possibility of developing a mechanism for regulatory alignment in OTC drug profiles. (Health Canada n.d.)
Contact: Janice Adams–King, Regulatory Health Project Manager, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research
Email: janice.adams-king@fda.hhs.gov

Over-the-Counter (OTC) Drug Review—Internal Analgesic Products

RIN: 0910-AF36 **Priority:** Economically Significant
Regulatory Flexibility Analysis Required: Yes
Legal Deadline: None
Timeline:

- NPRM (Amendment) (Required Warnings and Other Labeling) 12/26/2006
  NPRM Comment Period End 05/25/2007
- Final Action (Required Warnings and Other Labeling) 04/29/2009
- Final Action (Correction) 06/30/2009
- Final Action (Technical Amendment) 11/25/2009
- NPRM (Amendment) (Acetaminophen) 12/00/2014
- NPRM (Amendment) (Pediatric) 12/00/2014

Summary: This review establishes conditions in which OTC drugs are considered safe and effective. After the final rule, only OTC drugs meeting the conditions can be legally marketed. The first action addresses acetaminophen and the second (0910-AG12) addresses children's weight- and age-based dosing under two years old.
Contact: Janice Adams–King, Regulatory Health Project Manager, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research
Email: janice.adams-king@fda.hhs.gov

Over-the-Counter (OTC) Drug Review--Pediatric Dosing for Cough/Cold Products

RIN: 0910-AG12 **Priority:** Economically Significant
Regulatory Flexibility Analysis Required: Yes
Legal Deadline: None
Timeline: NPRM 11/00/2013
Summary: This is the second action to 0910-AF36 ad-

Continues on page 94.

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HHS Releases its Semiannual Regulatory Agenda

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dressing weight- and age-based dosing for children under two years old. This review establishes conditions required for OTC drugs to be considered safe and effective, therefore legal to market.

Contact: Janice Adams-King, Regulatory Health Project Manager, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research

Email: janice.adams-king@fda.hhs.gov

Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products

RIN: 0910-AG94 **Priority:** Other Significant

Regulatory Flexibility Analysis Required: Yes

Legal Deadline: None

Timeline: NPRM 09/00/2013

Summary: This rule proposes an amendment to regulations regarding New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Biologics License Applications (BLAs). This proposal would revise and clarify procedures for changing labels of approved drugs reflecting new information prior to the FDA's review of changes. This rule also would detail the process of a Changes Being Effected (CBE) labeling supplement and clarify requirements to submit conforming label revisions subsequent to FDA action.

Contact: Janice L. Weiner, Senior Regulatory Counsel, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research

Email: janice.weiner@fda.hhs.gov

Electronic Distribution of Prescribing Information for Human Prescription Drugs Including Biological Products

Decoding the Agenda

RIN: The regulation identification number (RIN) is a unique and unchanging 4-digit agency code plus a 4-character alphanumeric code assigned to all actions published in the Unified Agenda. (Center for Effective Government n.d.) (Office of Information and Regulatory Affairs n.d.)

Title: Each agency titles the rules published in the Unified Agenda. Unlike the RIN codes, titles may change over the course of a rule's lifecycle. (Center for Effective Government n.d.)

Abstract: The Unified Agenda includes agency summaries on the purpose and intention of a rule. More specific and substantial explanations of the agency actions will be published in the Federal Register. (Center for Effective Government n.d.)

Priority: Each agency determines the significance of the pending regulation.

- *Economically Significant* – greater than $100million annual effect
- *Other Significant* – considered substantial on public interest
- *Substantive/Nonsignificant or Routine and Frequent* – rules designated for review by the Office of Information and Regulatory Affairs (OIRA). (Center for Effective Government n.d.)

Major: Agencies and OIRA determine if rules are *economically significant* (> $100 million) and therefore, "major". Major rules require a Regulatory Impact Analysis (RIA) and must be approved by the Office of Management and Budget (OMB). (National Archives n.d.)

NPRM: A notice of proposed rulemaking (NPRM) announces the intent of an agency to publish a proposed rule in the *Federal Register*.

Unfunded Mandates: If expenditures are expected to exceed $ 100 million, agencies must evaluate costs and advantages of the mandate before publishing a Notice of Proposed Rulemaking. (Center for Effective Government n.d.)

CFR Citation: The parts of the Code of Federal Regulations (CFR) that are expected to be modified. The CFR classifies and codes general and permanent rules for publication in the Federal Register. (Center for Effective Government n.d.)

Legal Authority: Sections of the United States Code that give the authority to proceed with rulemaking.

Legal Deadline: Deadlines imposed on agency actions through the authorizing legislation or court orders.
v**Timetable:** Indication of actions, Federal Register citations, and projected deadlines.

Regulatory Flexibility Analysis Required: Rules with significant economic impact must prepare a Regulatory Flexibility Analysis (RFA) to evaluate less complex compliance approaches for smaller organizations.

Government Levels Affected: Agencies must analyze the federal, state, and local impact of regulatory actions.

Small Entities Affected: Implications in regards to small businesses, small governmental jurisdictions, and other small organizations.

Federalism: The determination of whether a regulatory action disrupts the authoritative distribution of federal, state, and local governments.

Agency Contact: Each entry in the Unified Agenda requires an agency contact.

Included in the Regulatory Plan: Each agency must prepare an anticipatory Regulatory Plan of the most significant regulatory actions. Each rule included in the plan require a statement of need, summary of legal basis, alternative propositions, and anticipated costs, benefits, and risks.

HHS Releases its Semiannual Regulatory Agenda

Continued.

RIN: 0910-AG18 **Priority:** Economically Significant
Regulatory Flexibility Analysis Required: Yes
Legal Deadline: None
Timeline: NPRM 01/00/14
Summary: In lieu of paper, this rule proposes the requirement of electronic packaging inserts for human drug and biological prescription products. The inserts would ensure the most up-to-date safety and efficacy information for healthcare practitioners.
Contact: Megan Velez, Policy Analyst, Department of Health and Human Services, Food and Drug Administration, Office of Policy
Email: megan.velez@fda.hhs.gov

Final Rule Stage

Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Pregnancy and Lactation Labeling

RIN: 0910-AF11 **Priority:** Other Significant
Regulatory Flexibility Analysis Required: Yes
Legal Deadline: None
Timeline:
- NPRM 05/29/2008
- NPRM Comment Period End 08/27/2008
- Final Action 05/00/2014

Summary: This final rule amends the Use in Specific Populations subsection content and format in regards to pregnancy, labor and delivery, and nursing mothers. The purpose is to better communicate risk in the labeling for human prescription drug and biological products.
Contact: Molly Flannery, Regulatory Counsel, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research
Email: molly.flannery@fda.hhs.gov

Combinations of Bronchodilators with Nasal Decongestants or Expectorants; Cold, Cough, Allergy, Bronchodilator, and Anti-asthmatic Drug Products for Over-the-Counter Human Use

RIN: 0910-AF33 **Priority:** Substantive, Nonsignificant
Regulatory Flexibility Analysis Required: Yes

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Janet Woodcock Includes ISPE in FDA Statement to Congress

On December 12, 2013, Janet Woodcock, Director of the US FDA's Center for Drug Evaluation and Research presented "FDA Check Up: Drug Development and Manufacturing Challenges" to the U.S. Congressional Committee on Oversight and Government Reform's Subcommittee to Energy Policy, Healthcare and Entitlements. In her address, Dr. Woodcock disclosed that although the United States is a global industry leader in pharmaceutical breakthroughs, it is no longer in the forefront of drug manufacturing.

Environmental hazards and low-cost foreign labor have resulted in final drug products, as well as their ingredients, being taken from overseas sources. Foreign-sourced materials have exposed multiple vulnerabilities and forced reactive measures for critical drugs needed for US patients. Dr. Woodcock discussed examples of FDA interventions preventing shortages due to sudden non-US supplier's discontinuance of ingredients, irreproachable shipping difficulties, and other unanticipated events. She also referenced ISPE's Drug Shortages study identifying inadequate manufacturing capabilities and the essential updates needed to counteract critical drug supply shortfalls.

The FDA, Dr. Woodcock continued, recognizes the need to modernize US drug manufacturing, but admits the Agency cannot revive the pharmaceutical sector alone. Woodcock described the FDA collaboration with industry experts in regard to stimulating new manufacturing technologies and quality systems. Enhancing development capabilities and reducing manufacturing costs, while continuing to safeguard patient safety is a goal both regulators and manufacturers share. Dr. Woodcock strongly advocated the use of Quality by Design (QbD) to accomplish this mutual goal. She supported her statement with the results of a survey conducted by the ISPE United Kingdom's Affiliate Process Analytical Technology (PAT) Community of Practice. Companies in this survey improved the vitality of product quality, increased process capability with speed and reliability, and benefitted from significant cost benefits through QbD. Manufacturing failures were identified and root causes modified before patient safety and economic investment were compromised.

Through studies, such as those initiated by ISPE, the FDA is discovering and supporting the results of modern manufacturing practices. Although some manufacturers are reluctant to restructure, Dr. Woodcock is optimistic that by educating facility stakeholders with proven studies, they will recognize the benefits of the modern advancements available in lifecycle improvement. The FDA is confident in the future of pharmaceutical manufacturing and strategically supports this transformative thinking and gradual evolution of cost-efficient and consistent quality.

References

1. Woodcock, Dr. Janet, "FDA Check Up: Drug Development and Manufacturing Challenges," FDA Congressional Testimony, Washington, D.C., 12 December 2013.

HHS Releases its Semiannual Regulatory Agenda

Continued from page 95.

Legal Deadline: None
Timeline:

- NPRM (Amendment)	07/13/2005
- NPRM Comment Period End	11/10/2005
- Final Action (Technical Amendment)	03/19/2007
- Final Action	06/00/2014

Summary: This final rule addresses cough and cold products containing an oral bronchodilator with a combination of expectorant or nasal decongestant. This action establishes the safe and effective conditions required in order to legally market the product.
Contact: Janice Adams-King, Regulatory Health Project Manager, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research
Email: janice.adams-king@fda.hhs.gov

Use of Certain Symbols in Labeling

RIN: 0910-AG74 **Priority:** Other Significant
Regulatory Flexibility Analysis Required: Yes
Legal Deadline: None
Timeline:

- NPRM	04/19/2013
- NPRM Comment Period End	06/18/2013

Concludes on page 97.

HHS Agenda

Continued from page 96.

- Final Action 04/00/2014

Summary: The purpose of this final rule is the allowance of FDA recognized, stand-alone symbols to be used under the condition a glossary accompanies the medical device.
Contact: Mary Follette Story, Human Factors and Accessible Medical Technology Specialist, Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health
Email: molly.story@fda.hhs.gov

Long Term Actions

Amendment to the Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals--Second Phase

RIN: 0910-AG20 **Priority:** Other Significant
Regulatory Flexibility Analysis Required: Yes
Legal Deadline: None
Timeline: NPRM 11/00/2014
Summary: The FDA will revise regulations for current Good Manufacturing Practices (cGMPs). The update and alignment of manufacturing controls will ensure quality, risk management, and the safety of raw materials.
Contact: Paula Katz, Regulatory Counsel, Office of Compliance, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research
Email: paula.katz@fda.hhs.gov

Amendments to the Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals--Components

RIN: 0910-AG70 **Priority:** Economically Significant
Regulatory Flexibility Analysis Required: Yes
Legal Deadline: None
Timeline: NPRM 11/00/2014
Summary: FDA revised regulations for current Good Manufacturing Practice' in finished pharmaceuticals.
Contact: Brian Hasselbalch, Consumer Safety Officer, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research
Email: brian.hasselbalch@fda.hhs.gov

References

1. Office of the Federal Register. 2014. Federal Register: The Daily Journal of the United States Government. https://www.federalregister.gov/articles/2014/01/07/2013-29632/regulatory-agenda.

Background of Quality Metrics

To view the Quality Metrics Whitepaper visit: http://www.ispe.org/quality-metrics-initiative.

The FDA has made *quality* a top priority for 2014. Under Janet Woodcock's personal direction, the proposed Office of Product Quality will embrace its principal of "one voice" for regulating drug quality. The FDA's goal is to ensure all pharmaceuticals, including generics and over-the-counter drugs meet high quality standards throughout the product's entire lifecycle. As of now, pharmaceutical manufacturing lacks a defined status of quality. As part of the reorganization of the FDA's quality expectations, they are proposing a metric-based surveillance to measure the state of quality in the industry. Their first step toward a "desired state" is to define the quality metrics essential to optimal pharmaceutical manufacturing. The anticipated collection of data would occur prior to an inspection and proposals also include risk-based inspections. An official release for the guidance on quality metrics should be available by the end of 2014 beginning a process of comprehensive quality data collections in 2015.

Since the FDA first documented the subject of quality metrics in the Food and Drug Administration Safety and Innovation Act (FDASIA), ISPE has led the way bringing industry and regulators together on the topic of quality metrics. The industry's first public discussions on quality metrics took place at ISPE's CGMP Conference in June 2013 during an interactive workshop led by Cindy Salamon, VP, Global Quality Services, Bristol-Myers Squibb and Russell Wesdyk, Science Coordinator, US FDA. Conversations resumed at ISPE Annual Meeting in November 2013 with Salamon and Wesdyk returning with updates on further perspectives from the FDA and their regulators. At the request of the FDA, a whitepaper was prepared for a December presentation based on the discussions and presentations from both ISPE's CGMP Conference and ISPE's Annual Meeting.

ISPE's Quality Metrics Project

ISPE's Product Quality Lifecycle Implementation (PQLI)-sponsored Quality Metrics project team, consisting of representatives from various pharmaceutical companies, began the proposal with an initial list of reportable site-based quality metrics. Wesdyk defined a quality metric as "an objective measure relevant to the quality of a product, site, or system. From FDA's perspective ideal quality metrics would be:

- Objective and quantitative
- Relevant and applicable across sectors
- Understandable and operational
- Meet FDASIA 704 and 706 regulatory requirements

ISPE Proposals for FDA Quality Metrics Program – Whitepaper Summary

ISPE Metrics

The ISPE team generated several refined indicator metrics to parallel the FDA's "six systems" inspection program. Table 1 of the whitepaper gives metrics proposed initially for evaluation in a suggested Phase 1 of the program.

Scope

A site is in scope if it performs any cGMP unit operation for a drug substance or a product included in a drug commodity sourced to the US. It is suggested the option for a company to submit either:

- Metrics for all products manufactured at that site since metrics are often collected on a site basis
- Metrics for unit operations for those products supplied to the US

Definitions

Table 2 of the whitepaper gives proposed draft definitions of metrics.

Data Submission

Sites within scope report should report annually to the FDA by the end of February. The industry would provide the raw data and proposed metric. It is not proposed to submit products registered by site.

Algorithm(s)

It is anticipated that FDA and industry representatives cooperate to develop a suitable algorithm(s).

Evaluation of Metrics

The ISPE Quality Metrics project team has found challenges in comparing metrics between companies related to:

- Definitions and interpretations
- Ability to provide data in consistent and manageable formats
- Consistent analysis across sites from different technologies

Further work is recommended to develop less complex processes and instruments for data evaluation.

Alternative Metrics Considered

1. Quality System Effectiveness
2. Process Capability
3. Quality Culture Index

Concludes on page 99.

Background of Quality Metrics

Continued.

Principles

Metrics must meet the need of supporting a FDA risk-based inspection program and drive acceptable behavior by both industry and regulators. Acceptable metrics must be:

- Measures of quality and/or compliance
- Defined for consistent reporting
- Objective and significant
- Nonintrusive and time efficient
- Normalized
- Drive acceptable

Next Step Options

ISPE's Quality Metrics project team proposes a pilot program in cooperation with the FDA for multiple phases focused on the following goals:

- Examining and gathering feedback on the process of collecting, analyzing, evaluating and reporting the data
- Clear definition discrepancies in terminology/language
- Clear unintended consequences

ISPE recommends nine months (two sets of quarterly measures) of data collection for the pilot program. Additional recommendations by initiative team include:

- FDA and industry representatives should design program and evaluate data.
- Variety of operations should be evaluated with different unit operations, size, location, and product.
- Companies retain access to their own data and potentially summaries of all data
- Implementation of a single pilot program

Conclusion

Although there are many challenges initiating a program of quality metrics that both industry and regulators agree upon, ISPE is willing to support the pilot program with the proposal outlined in the Quality Metrics Initiative Team's whitepaper.

Quality Metrics Team

Cynthia Salamon (Team Leader), Bristol Myers Squibb
Ferdinando Aspesi, Novartis
Michael Davidson, Pfizer
Joseph Famulare, Genetech/Roche
Diane Hagerty, Genetech/Roche
Lorraine McClain, Teva Pharmaceuticals
Lorraine Thompson, Novartis

Excitement Builds for 2014 Facility of the Year Awards

The 2014 Facility of the Year Awards (FOYA) is shaping up to be one of the most noteworthy events of the year. FOYA is celebrating its tenth year as the industry's premier global awards program recognizing innovation and creativity in manufacturing facilities serving the regulated healthcare industry. To mark the occasion, ISPE has introduced a number of enhancements to the 2014 program.

One of these enhancements is already building industry buzz, the brand-new Facility of the Year Awards Banquet. The 2014 Category Winners (who will be announced the week of 21 March) will be recognized during this gala event, which will be held on 3 June 2014 in Baltimore, Maryland USA, in conjunction the third annual ISPE-FDA CGMP Conference and ISPE's Global Pharmaceutical Quality Week.

The timing for this event is significant; as ISPE CEO Nancy Berg said in a press statement when the banquet was announced in late 2013:

"Over the past decade, the pharmaceutical and biopharmaceutical industry has made significant advancements in the technology and processes used in building and renovating manufacturing facilities... reflect[ing] the industry's quest for excellence and superior product quality. As the premier awards program focused on recognizing these achievements, it is only fitting that the Facility of the Year Awards also make advancements in the way it showcases the Category Winners' momentous accomplishments. By bringing the annual celebratory events for FOYA to Pharmaceutical Quality Week, ISPE will present these innovative facilities to a global audience of top pharmaceutical leaders and regulators."

For the first time in the history of the awards program, a limited number of tables are available for sponsorship by companies who wish to show their support for the 2014 Category Winners' commitment to excellence. Individual tickets will also be available to those who wish to attend the banquet and hear from the winners in their first public appearance of the year. More information about the banquet is available at www.FacilityoftheYear.org.

The Category Winners will also be represented in a display area dedicated to showcasing their achievements during the CGMP Conference. Attendees of the conference will have the opportunity to speak one-on-one with representatives of the winning companies to discuss their projects and ask questions about the specific innovations in their respective facilities.

The CGMP FOYA display area and the Facility of the Year Banquet will both feature retrospectives of the program's 10-year history. These special presentations will look back at past winners and examine how FOYA has contributed to industry's overall progress in technological advancements.

In addition to the recognition planned during Pharmaceutical Quality Week, there will be FOYA celebrations planned during the Society's largest events of the year, the 2014 Annual Meeting, 12 – 15 October in Las Vegas, Nevada USA, and Pharma EXPO, 2 – 5 November in Chicago, Illinois USA. Details about FOYA activities at these events will be available in coming months—stay tuned!

New Quality Culture...

Continued from page 90.

future challenges. Key Points of Track Three:

- Introducing new technology solutions
- Implementing operational excellence
- Discovering opportunities in regulatory changes

Participants can expect up-to-date knowledge and practical experience in regards to moving pharmaceutical facilities into the future through more efficient logistics and technologies. Track Three will explore altering current manufacturing without a complete rebuilds and disclose how CMOs have successfully challenged the flexibility at their facility. Track Three attendees will also discover what happens in the suppliers' development labs that would move a company toward a less costly, more efficient facility.

Conclusion

The Quality of Culture movement will be an empowering implementation for the entire pharmaceutical industry. It is important to appreciate the benefits of this new proactive mindset and recognize the risks of remaining reactive. Transforming an industry requires education and commitment. The New European Conference: *Driving Effectiveness in Pharmaceutical Operations with the new Quality Culture* was specifically developed by ISPE to inspire manufacturing pacesetters and assist the evolution to a new future of quality. Why should you attend? Zimmer, gives one undeniable reason, "As the future will be discussed!" Look ahead with ISPE and find the *Quality of Culture* within your company.

HONORING INNOVATION

The Facility of the Year Awards Banquet

Tuesday, 3 June 2014
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Reception at 18.30
Program begins at 19.30

Join ISPE and prominent industry leaders as we recognize the 2014 Category Winners and celebrate 10 years of industry innovations in facility design, construction and operation that have led to improved product quality and enhanced patient health.

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For the first time in FOYA history, award banquet sponsorships, tables and individual tickets are available. Contact Alisa Pachella at +1-813-739-2274 or apachella@ispe.org to reserve your space today! Also ask Alisa about opportuities in the FOYA supplement.

www.FacilityoftheYear.org

Japan Affiliate "On the Road" Again

by Shigeru Nakamura and Michael J. Lucey

The "2013 US Pharmaceutical Plant Tour" by the Japan Affiliate included six plant visits, a networking reception, dinner presentation by former FDA, and participation by all travelling members in the ISPE Annual Meeting in Washington DC. The total itinerary called for departure from Japan on 27 October and return on 8 November.

Organized by Shigeru Nakamura, Affiliate Vice Chairman, and Michael Lucey, Adjunct Director, with the close support of four Board Members, the group comprised 22 members: eight from pharmaceutical manufacturers, 10 from engineering companies, two from construction firms, and two from equipment fabricators.

Boehringer Ingelheim (BI)

Boehringer Ingelheim Roxane, located in a central area of Columbus, functions as an important center for BI production. The high-containment operations (HCO) plant visited on this tour has a dedicated building built on the extensive site for the production of a large variety of products in a wide range of batch sizes.

Morphotek (2013 Facility of the Year (FOYA) Sustainability Category Winner)

Located in Exton, Pennsylvania, Morphotek, a US subsidiary of Eisai Co., Ltd., a leading Japanese pharmaceutical manufacturing company, is remarkable for its sustainability-oriented architectural design and environmental management realized at its Pilot Manufacturing Plant. The facility supports the manufacturing of advanced therapeutic candidates with either cell culture or microbial systems.

Genzyme

The Ridgefield plant of Genzyme, located approximately 40 minutes' drive from New York, began operations in 1983 and expanded its facilities in 2009. This impressive facility is a multi-product manufacturing plant, with its focus on syringe filling. As with all of the US host organizations, the Japan Affiliate was very well cared for, with outstanding explanations and noontime hospitality.

Novartis (2013 FOYA Overall Winner)

A highlight of this plant tour was the visit to Novartis which was to be the 2013 FOYA Overall Award winner. Located in Holly Springs, North Carolina, the plant visited is a cell culture facility for influenza vaccine production, with its mission being to secure a supply of influenza vaccine for a great number of people throughout the US within six months in the event of pandemic influenza.

Biogen Idec (2013 FOYA Facility Integration Category Winner)

Located in Research Triangle Park (RTP), North Carolina, Biogen Idec constructed its Flexible Volume Manufacturing Facility (FVM), for the manufacture of multiple products, flexibly responding to requirements such as "smaller batch sizes," "batch size changes," and "shorter manufacturing periods." The facility features a 100% single use flow path in a validated closed system, giving the impression that the US, compared with Japan, was advanced in the application of "single use" technology.

MEDIMMUNE (2011 FOYA Overall Winner)

Completed in 2010, MedImmune's Frederick Manufacturing Center (FMC) expansion facility, the biologics arm of AstraZeneca, is a large-scale mammalian cell culture-based production facility. For the minimization of human errors, an advanced and intensive education and training program based on simulation control panels ensures that operators are most effectively transitioned to the facility. It was the great pleasure of the Japan Affiliate to be received at Frederick for this return visit.

A yearly feature of the Plant Tour is a networking reception with a US Chapter nearby to a plant visited. The New Jersey Chapter made a special effort to receive the visitors from Japan. Introductions were provided of the activities of Chapter and Affiliate. Tour members spent an exceptionally pleasant time in a friendly and informative setting.

On behalf of the tour participants, deep gratitude is expressed to all concerned at the organizations which so willingly and thoroughly accepted the plant visits, as well as to the good people of the NJ Chapter for their hospitality.

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