The Official Magazine of ISPE

MAY/JUNE 2015 VOLUME 35, NUMBER 3

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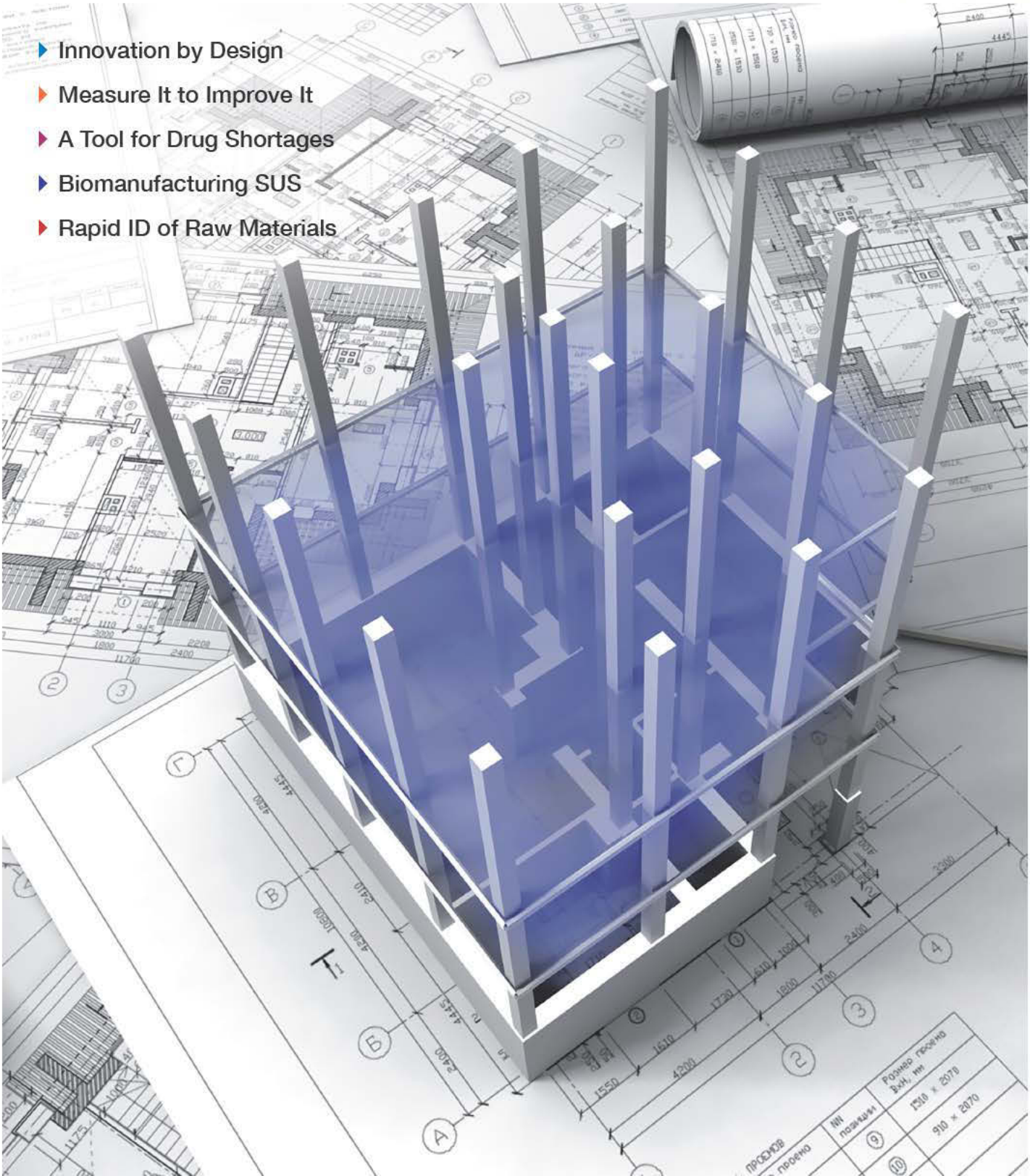

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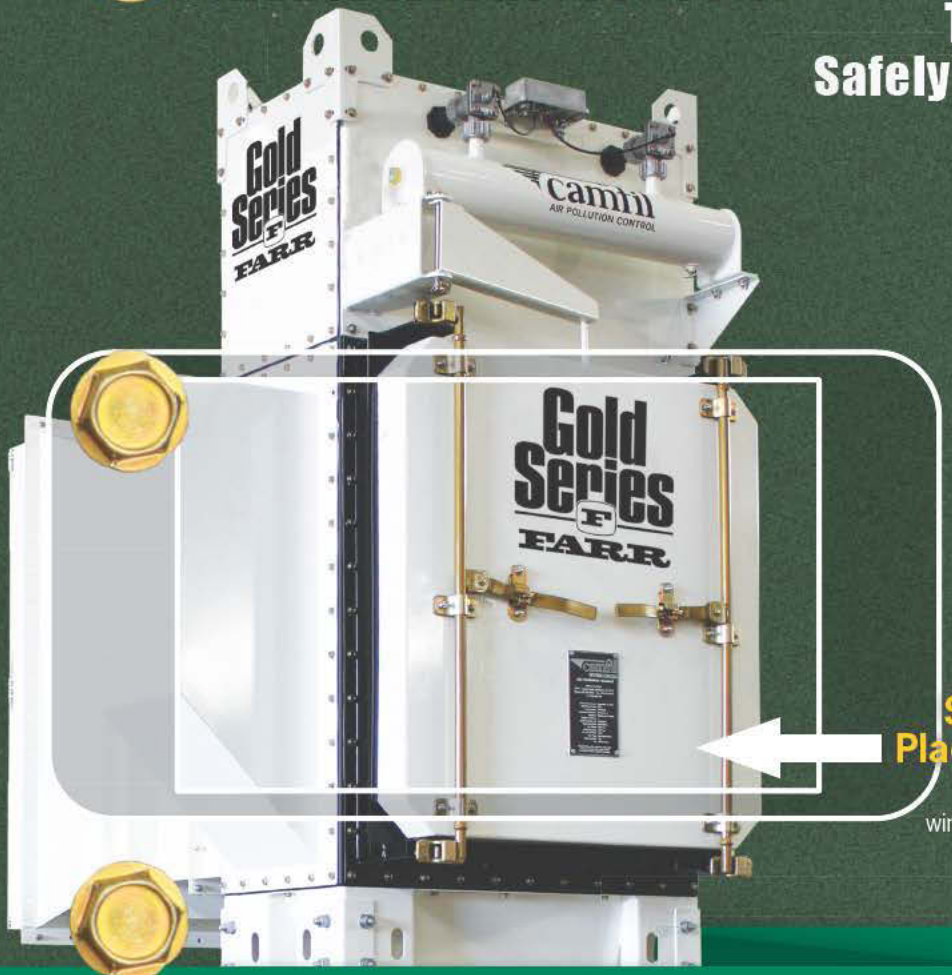



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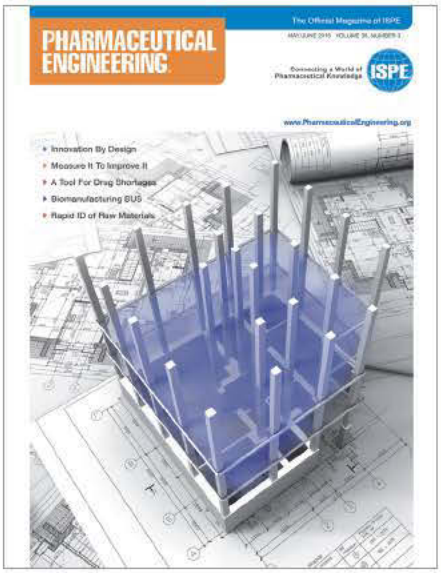


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"*Patient Safety is #1*" was the mantra this year's FOYA Honorable Mention recipient, Pharmalucence, repeated through the process of executing on its dream of an integrated facility that provides a blueprint for solving the legacy facility, legacy product, drug shortages problem. It is a mantra that also precipitated the innovation of synthetic insulin, late last century. How our members incorporate the notion of patient safety into all aspects of pharmaceutical manufacturing processes, products and facilities is what FOYA strives to recognize and celebrate. Now on the cusp of its 12th year, ISPE's FOYA program is more committed than ever to the pursuit of innovation that improves patient safety in all its forms.

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## ISPE UPDATE



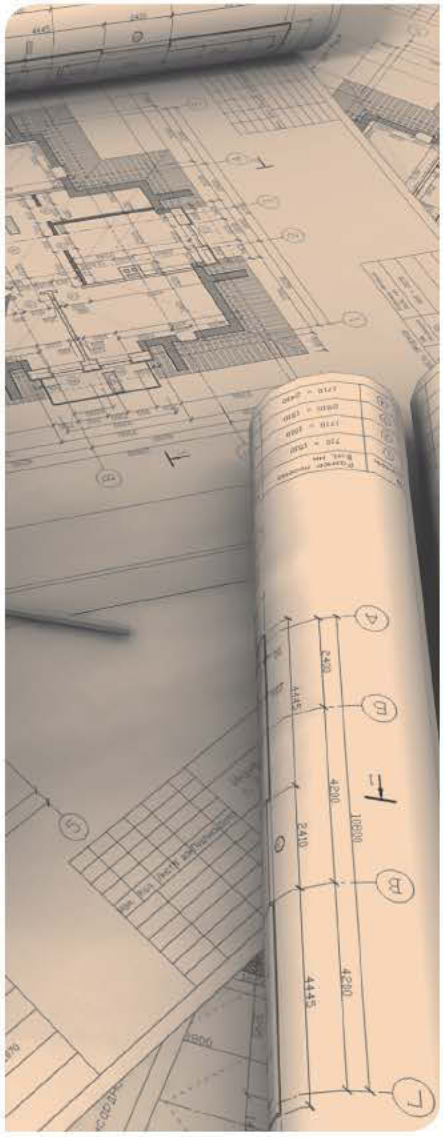
## FACILITIES AND EQUIPMENT



## REGULATORY COMPLIANCE



## PRODUCTION SYSTEMS



## Editor's Note

In the March/April 2015 issue, the biography for Orlando López, author of "A Computer Data Integrity Compliance Model" should have read:

Orlando López is a Data Integrity SME with over 25 years of experience of worldwide medicines and medical devices computer systems regulatory compliance. His special interest is the GMP compliance issues applicable to computer systems. López is the author of two books: "21 CFR Part 11 – A Complete Guide to International Compliance," published by Sue Horwood Publishing Limited and "Computer Infrastructure Qualification for FDA Regulatory Industries," published by Davis Healthcare International Publishing. He is currently writing his third book on computer systems validation using the EU Annex 11 which will be published by CRC press early 2015.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## JUNE 2015

**01–03 ISPE/FDA/PQRI Quality Manufacturing Conference, Washington, DC, US**

**02 2015 ISPE FOYA Banquet, Washington, DC, US**

02 Boston Area Chapter, Young Professionals Red Sox Game, Boston, Massachusetts, US

11 Belgium Affiliate, Round Table Discussion Mobile Application, Puurs, Belgium

11 France Affiliate, Data Integrity, Paris, France

11 Nordic Affiliate, Cleaning Network Meeting, Valby, Denmark

11–12 Poland Affiliate, Changes in Pharmaceutical Law, Warsaw, Poland

12 South Central Chapter, Oklahoma City Brewery Tour, Oklahoma City, Oklahoma, US

16 Canada Affiliate, Annual Golf Tournament Montreal, Quebec, Canada

25 Midwest Chapter, Dinner, Minneapolis, Minnesota, US

25 San Diego Chapter, CEO Night, San Diego, California, US

## JULY 2015

01 Spain Affiliate, Jornada de Biológicos, Barcelona, Spain

10 Italy Affiliate GDP Compliance and Cost Saving, Rapallo, Italy

16 San Francisco/Bay Area Chapter, Fun Day, Napa, California, US

23 San Diego Chapter, Networking Event, Maritime Museum, San Diego, California, US

## AUGUST 2015

06 San Diego Chapter, Vendor Night at Green Acre, San Diego, California, US

07 San Diego Chapter, Golf Tournament, San Diego, California, US

27 Midwest Chapter, Golf Event, St. Louis, Missouri, US

## SEPTEMBER 2015

03 Nordic Affiliate, Advance Aseptic Processing Event, Copenhagen, Denmark

03 San Diego Chapter, Networking Event Padres vs. Dodgers, San Diego, California, US

09 DACH Affiliate, GAMP COP Workshop, Frankfurt, Germany

10 Ireland Affiliate, Joint Event, Dublin, Ireland

**14–16 ISPE Philadelphia Training, Philadelphia, Pennsylvania, US**

16 Spain Affliate, Jornada de Fabricación Estéril, Barcelona, Spain

17 Spain Affiliate, Jornada de Fabricación Estéril, Madrid, Spain

17 Boston Area Chapter, Regulatory Compliance, Andover, Massachusetts, US

21–22 Canada Affiliate, Annual General Meeting, Ottawa, Ontario, Canada

22 Belgium Affiliate, Connecting the Dots with Statistics, Leuven, Belgium

22 Chesapeake Bay Area Chapter, Golf Tournament, Ijamsville, Maryland

24 France Affiliate Institut de Pharmacie Industrielle de Lyon (IPIL) Lyon, France

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24 San Francisco/Bay Area Chapter, Evening Meeting, San Francisco, California, US

**28–30 ISPE Barcelona Training, Barcelona, Spain**

**28–30 2015 Pharma EXPO, Las Vegas, Nevada, US**

30 Nordic Affiliate, Biotech Event, Strängnäs, Sweden

## OCTOBER 2015

**07–08 ISPE Process Validation Conference, Silver Spring, Maryland, US**

07 Boston Area Chapter, Annual Product Show, Foxboro, Massachusetts, US

07 San Diego Chapter, Clinical to Commercial Meeting, San Diego, California, US

12 DACH Affiliate, Wassersysteme in Der Pharmaproduktion, Weinheim, Germany

13 Belgium Affiliate, GAMP Benelux COP Data Integrity, Zwijndrecht, Belgium

15 Nordic Affiliate, PAT (1 day), Copenhagen, Denmark

**19–20 ISPE Raleigh Training, Raleigh, North Carolina, US**

19–23 ISPE Boston Training Series, Boston, Massachusetts, US

21 Spain Affiliate, Jornada de GAMP y Automatización, Barcelona, Spain

22 Spain Affiliate, Jornada de GAMP y Automatización, Madrid, Spain

22 San Diego Chapter, Joint Facilities Reception Biocom and IFMA, San Diego, California, US

29 Midwest Chapter, Halloween and Get Pumped for Annual Meeting Party, Kansas City, Missouri, US

## NOVEMBER 2015


**08–11 ISPE Annual Meeting**

**Philadelphia Marriott Downtown Philadelphia, Pennsylvania, US**

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# ISPE 2015 TRAINING

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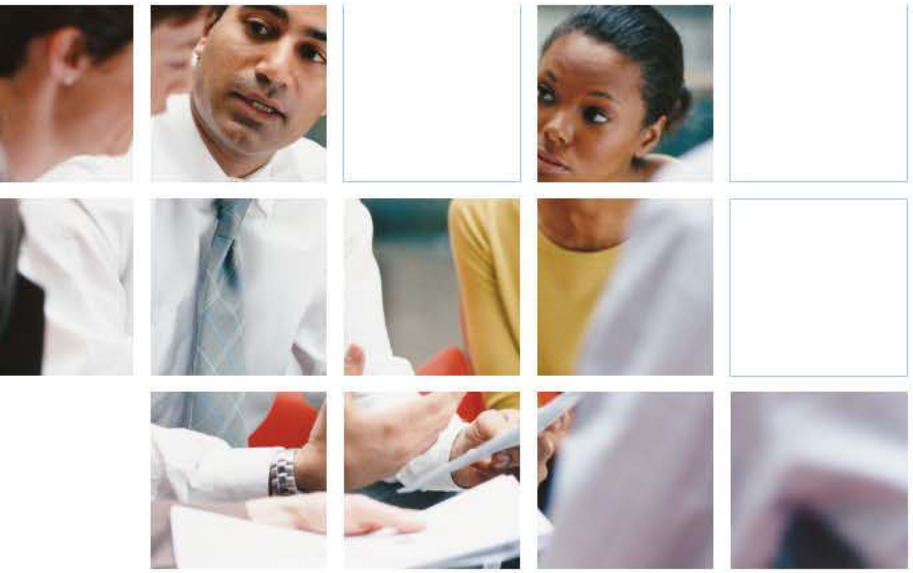

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## 19-20 October
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## 19-23 October
Boston, MA • The Inn at Longwood Medical

## 9-10 November
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## 7-10 December
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- Applying Quality Risk Management (T42)
- Applying the Biopharmaceutical Manufacturing Facilities Baseline® Guide Principles (T31)
- Basic GAMP® 5, Annex 11 and Part 11 – Update (T45)
- Cleaning Validation (T17) – **Updated course includes new guide!**
- Facility Project Management (T26)*
- HVAC (T14)
- Managing the Risk of Cross Contamination (Risk-MaPP) (T41)
- Oral Solid Dosage Forms (T10) – **Updated course and guide!**
- Pharmaceutical Water Generation (T04) – **Updated course and guide!**
- Practical Implementation of Process Validation Lifecycle Approach (T46) – **New course!**
- Process Validation in Biotechnology Manufacturing (T32)
- Q7A: Implementing Good Manufacturing Practices (T30)
- Risk-Based Verification of Facilities, Systems and Equipment Workshop (T48)
- Sterile Product Manufacturing Facilities (T12)
- Storage Delivery and Qualification of Pharmaceutical Waters (T23) – **Updated course and guide!**
- Turning QbD into a Practical Reality (T43)

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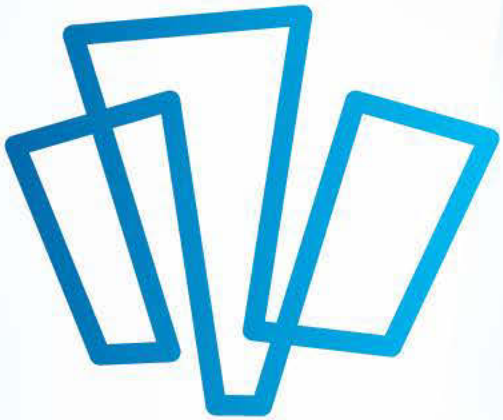

# FOYA 2016

## Facility of the Year Awards

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# CELEBRATING PURPOSE, INTENT AND INNOVATION

> Always design a thing by considering it in its next larger context – a chair in a room, a room in a house, a house in an environment, an environment in a city plan.
>
> *Eliel Saarinen*

***John E. Bournas***
***President and CEO, ISPE***

**Innovation can come in many forms.** And you never know when a particular breakthrough will change the world. Indeed, history is replete with the legacies of innovators who have reinvented the rules using science and the power of their imaginations. As Eliel Saarinen said, "Always design a thing by considering it in its next larger context—a chair in a room, a room in a house, a house in an environment, an environment in a city plan".

Just think of the areas of manufacturing, design and engineering; individuals with a vision and a passion to effect change have shaped the world we know today. People like Ray and Charles Eames, designers who influenced the way we make chairs. Like Henry Ford, who perfected the concept for an assembly line and manufactured the first affordable car. Or architects like Zaha Hadid and Oscar Niemeyer, who have designed and erected buildings that defy gravity, as well as convention.

Regardless of the industry, these individuals share a common trait. Each of them took matter that would not bend to established standards—whether it was plywood, metal, concrete or light—and shaped it to suit their respective visions. Their clarity of intention fuelled their resolve and ultimately, their success. They redefined what was possible.

In many ways, our FOYA winners share that trait as well. Perhaps they have not yet reached the dizzying heights of the innovators I mentioned above. But who is to say that one day, one won't? Or, perhaps, not enough time has passed for us to truly appreciate the greatness of their innovative processes, projects and products.

Vision begets innovation. At ISPE, we want to see our vision of a world without drug shortages inspire engineers around the world to find solutions. And why shouldn't we?

ISPE's members work in an industry where ideas lead to the creation of medicines; an industry that manufactures medicines to create possibilities; and an industry that can positively impact people's lives. That is its essential purpose and it is achieved through collaboration with a broad spectrum of stakeholders from the pharmaceutical industry, regulatory agencies, health organizations and patients.

ISPE's FOYA program, too, fosters collaboration. The FOYA winners represent the collaborative efforts of engineers, architects, designers,contractors and suppliers. On the surface, their efforts had positiveimpact on their organizations by increasing manufacturing efficiency, reducing costs and lead times, or helping reach new clientele. However, from ISPE'S perspective, the fruit of their efforts runs deeper than that. Their efforts support an underlying purpose that all ISPE members share—to ensure quality medicines reach the people who need it, when they need it, anywhere in the world.

FOYA was created just over a decade ago to celebrate six facets of manufacturing excellence: *Project Execution, Facility Integration, Equipment Innovation, Sustainability, Process Innovation and Operational Excellence*. Each of the FOYA categories stands on its merit, yet each embodies a form of innovation. It is that common purpose, intent and innovation that we celebrate through FOYA.

# FOYA CATEGORY WINNERS TO BE HONORED AT 2015 ISPE FACILITY OF THE YEAR AWARDS BANQUET

**The recently announced 2015 ISPE Facility of the Year Awards (FOYA) Category winners will receive their awards at the 2015 ISPE Facility of the Year Awards Banquet on 2 June 2015 in Washington, DC. The banquet is being held in conjunction with the ISPE/PQRI Quality Manufacturing Conference.**

**Astellas Pharma Inc.**

Equipment Innovation
Tube Labeling Project
Killorglin County Kerry,
Ireland

**AstraZeneca China**

Project Execution
Taizhou Supply Site Project
Phase I
Taizhou, Jiangsu Province, China

Now in its 11th year, the FOYA program highlights the accomplishments, shared commitment and dedication of individuals in companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of patients around the globe. Each year, a global judging panel examines the submitted proposals and designates winners in specific categories, when merited.

This year's winners include projects in three categories—*Project Execution, Equipment Innovation and Facility Integration*—plus one *Honorable Mention*. Their scopes were as varied as the end-user products they produced. From detailed planning in the construction of a new facility to the invention of a new tube labelling process, and from building on in-house expertise to enter new market segments to the audacity to take calculated risks to succeed.

"Each of our 2015 Category Award winners has captured the spark of innovation and transformed it into processes, projects and products that ensure quality medicines reach the people who need it, when they need it, anywhere in the world," said ISPE President and CEO John E. Bournas. "The facilities honored as the 2015 ISPE FOYA Category Winners exemplify the ideals of the FOYA program and ISPE's dedication to enhancing patient health through advancements in pharmaceutical manufacturing."

The judging panel did not award any projects in the *Sustainability, Process Innovation* and *Operational Excellence* categories this year despite having received a number of high-quality submissions. James A. Breen, Chair of the 2015 FOYA Judging Panel, explained that "several of the submissions met some of the criteria in these categories, yet merit had to be the defining criteria in choosing a FOYA Category Winner."

## 2015 FOYA Honorees

**AstraZeneca China** was the winner in the *Project Execution* category for its market supply solid dose facility located in Taizhou, China. Responding to the Chinese government's "Healthy China 2020" program, the company quickly took the necessary action to address this growing need.

AstraZeneca's in-country team tapped in to the company's global engineering, operations and safety practices in putting together a detailed project plan that focused on building a strong, well-integrated team where every individual understood their role in the overall project.

The results were extraordinary. The team managed to go from a farmer's field into a fully-functional pharmaceutical facility capable of manufacturing five billion tablets of high-quality, affordable medicines within only 20 months. In addition, the facility came in 18% under budget while maintaining an exemplary safety record of 3.26 million hours worked without a recordable safety incident.

The winner in the *Equipment Innovation* category was **Astellas Pharma, Inc.** is for its tube packaging and labeling equipment project. Tackling a truly inefficient process that required long lead times and the high cost of carrying numerous product language variations, the project team invented a new technology allowing it to print country-specific labels on pre-filled tubes.

The project had an international flair, with major contributions coming from Japan, Germany and Ireland. In the end, Astellas Ireland Co Ltd's Kerry plant implemented a technology innovation originating from the company's Japanese engineering team. Instead of following the industry standard of printing on empty tubes, the Astellas team came up with a process allowing it to add country-specific label information on pre-filled tubes that had only common printed information.

The team's innovation dramatically improved plant flexibility, simplified the supply chain, and significantly reduced acceptance testing, product raw materials stock levels and overall delivery lead-time.

**IDT Biologika**

Facility Integration
Multipurpose Biologics and Vaccines Production Facility (Isolator Vaccine Filling Unit)
Dessau-Rosslau, Germany

**Pharmalucence Inc.**

Honorable Mention
Aseptic Fill-Finish Facility
Billerica, MA, US

**IDT Biologika GMbH** was named the winner in the *Facility Integration* category for its biologics and vaccines production facility in Dessau, Germany. For almost 20 years, the company has been well-known for manufacturing live vaccines for both Phase 1 and Phase 2 clinical trials. In 2014, they responded to customer demand and completed a project that now allows them to manufacture for both late stage clinical trials and contract manufacturing for commercial supply.

The project team constructed a highly-automated manufacturing facility designed to be modular, efficient and expandable for filling and freeze-drying of vaccine products. The site's layout was devised to guarantee the shortest supply and disposal routes. Design of the integrated equipment suite made significant contributions, resulting in efficient product change over and increased efficiency.

The new facility expanded the company site in Dessau from two to three buildings and was designed with future expansion in mind.

**Pharmalucence Pharmaceuticals** received an *Honorable Mention* for the execution and entrepreneurial spirit demonstrated by the construction of its new aseptic filling facility in Billerica, Massachusetts, USA. Through good planning and prioritization, Pharmalucence met the challenge of balancing investment, appropriate compliance, efficient operations and business viability.

Following the company's foundation through a management buyout in 2007, Pharmalucence's management team recognized the inefficiencies of their current plant infrastructure. Despite the ongoing financial crisis, and with limited financial resources, management leveraged government incentives and capitalized on favorable real estate conditions in consolidating their legacy manufacturing facilities into a single, newly-constructed facility.

The project was an outstanding success, allowing the company to reinforce their current product lines and expand into the contract manufacturing realm. So successful, in fact, that the business and facility came to the attention of Sun Pharmaceutical, who moved to purchase the company in July 2014.

All of the 2015 FOYA Category Winners will be on site at the ISPE/PQRI Quality Manufacturing Conference in Washington, where attendees and delegates will have the opportunity to chat with the winning company's representatives about their projects.

### 2015 ISPE Facility of the Year Awards Judging Panel

James A. Breen, Jr.
Judging Panel Chair
Vice President, Worldwide Engineering-Technical Operations
Johnson & Johnson

Charles F. Calitri
Vice President, Global Engineering
Pfizer, Inc.

Chris Chen, Ph.D.
Senior Vice President and Chief Technology Officer, Biologics Service
WuXi AppTec Co. Ltd.

Antonio C. Crincoli, PE
Executive Director
Bristol-Myers Squibb

Francis W. DeMarinis
Senior Director, Central Engineering
Purdue Pharma LP

Brian H. Lange, PE
Executive Director, Global Supply Chain
Merck & Co Inc.

Paul T. Malinowski, PE, PMP
Director, Project Management & Engineering Services
Becton Dickinson and Co.

Emilio Rivera
Vice President, Engineering
Amgen Inc.

Gary S. Schoenhouse
Senior Director of Engineering
Genentech Inc.

Simon C. Shelley
Vice President Engineering, Primary Supply
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Sanjit Singh Lamba
Managing Director& Head of Global Procurement Strategy
Eisai Pharmatechnology & Mfg Pvt Ltd

Andrew D. Skibo
Regional Vice President, Supply Biologics, Global Engineering and Real Estate
MedImmune /AstraZeneca

The **2015 FOYA Overall Winner** will be announced during the plenary session at the 2015 ISPE Annual Meeting on **November 8–11** in Philadelphia, Pennsylvania.

# REPORT ON QUALITY METRICS SUMMIT

## Also in this section



Almost eleven months after the *ISPE Quality Metrics Pilot Program* kicked off on 2 June, 2014 at the ISPE-FDA CGMP Conference, the ISPE Quality Metrics Team, comprising volunteers from a variety of pharmaceutical companies working in partnership with McKinsey & Company, reported their findings from "Wave 1" of the program at the Quality Metrics Summit, held in Baltimore on 21–22 April, 2015.

The Summit served to give attendees, from both the industry and the FDA, an overview of the findings of the task force and to detail some of the specifics from Wave 1 of the program. Task force members explained how definitions were hammered out to assure that the metrics ultimately employed would be standardized. They also discussed finer details, such as how data was submitted and what the data "said" going forward in designing "Wave 2" of the program.

"Learnings" from Wave 1 were discussed at the end of the day Tuesday. "What's Next for Quality Metrics" was a topic discussed as the conference closed on Wednesday.

Two workshops held on Tuesday included specifics on data submission and definitions. Workshop attendees and leaders of the "definitions sub-committee" discussed the need to develop "clear and crisp" definitions that were "precise and harmonized" for measurements of Lot Acceptance Rate; Critical Complaints Rate; Recurring Deviations Rate; CAPA Effectiveness Rate, and other measurements and terms. Discussions in the data submission workshop suggested that it would be valuable to have a metrics training program for data submission, grace and verification periods established, standardized data collection templates, and ways to ensure data confidentiality.

Vanya Telpis and Paul Rutten of McKinsey & Company explained their role in defining terms as well as analyzing the patterns, relationships and implications presented by the data. Some relationships were "surprising" said Rutten, while others were not.

During the Metrics Summit several speakers, from both industry and the FDA, reinforced the need for quality metrics to ensure product quality and patient safety.

In her Wednesday plenary address, Janet Woodcock, MD, Director, FDA/CDER, told attendees "you can't improve what you can't measure," and also reinforced that FDA, also working on developing metrics, appreciated ISPE's efforts and the data from Wave 1, adding "You are helping us" .

### Sharing Results of First Quality Metrics Pilot Program

*John Bournas, President and CEO, ISPE*
*Diane Haggerty, Vice President, Genentech*
*Willie A. Deese, Executive Vice President, Merck & Co.*
**Opening Plenary Session: 21 April**

John Bournas welcomed attendees and thanked both the companies participating in Wave 1 of the ISPE Quality Metrics Pilot Program for their expertise and enthusiasm and the ISPE Quality Metrics Task Force volunteers for their hard work.

"As you know, ISPE is committed to helping industry to identify and define metrics that are truly indicative of our intent when we first initiated discussion of quality metrics in June 2013," said Bournas. "An ISPE task force was organized to distill a list of metrics to promote quality and predict safety. We conducted the industry's first pilot metrics program and we are looking forward to sharing the results of the ISPE Quality Metrics Pilot Program Wave 1 today with industry and the FDA."

Bournas introduced Diane Hagerty, Vice President, Genentech Inc., and the Task Force co-chair. "It is exciting to finally have a dedicated conference for quality metrics," said Hagerty. "We are also excited about sharing outcomes of the pilot program and getting the data to industry."

Hagerty introduced Willie A. Deese, Executive Vice President, Merck & Co., who told attendees that Merck has spent the past five years improving quality through metrics and laid out some of the programs and steps the company has taken to achieve higher corporate quality.

"What is it like to be a patient?" asked Deese. "We have all been a patient or know someone who has been a patient. At the end of the day, what really matters is delivering what the patient needs when it is needed."

Deese discussed four elements employed at Merck: compliance, reliable supply, strategy, and budget. "The first two are the most important," he said. "We never make decisions based on budget. We link people to targets and make sure that everyone knows what we are measuring and why."

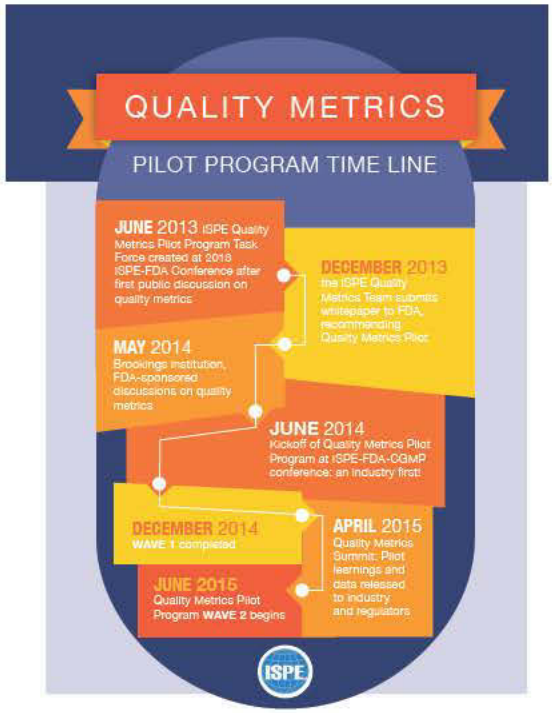
Ashley Boam, Acting Director, FDA/CDER/OPQ/OPPQ, spoke on how data from metrics may be used by the FDA to establish quality standards and expectations for industry and help make "robust analyses" of industry. "If you can't measure it, you can't manage it," said Boam, who also noted that it is important to develop quality metrics that are useful for both products and sites.

Boam suggested that quality metrics can lead to fewer recalls and fewer drug shortages, which are FDA goals for the industry. She thanked ISPE for their efforts in carrying out the ISPE Quality Metrics Pilot Program and noted that it has the potential to better protect the drug supply.

### "You Can't Improve What You Can't Measure"

*Janet Woodcock, MD, Director, FDA/CDER*
**Plenary Session: 22 April**

Dr. Woodcock spoke about a variety of issues regarding company quality culture and quality metrics, but began with a "thanks" to ISPE for embarking on a mission to bring quality metrics to the industry.




"Building a quality culture begins with a goal," Woodcock told attendees. She reviewed the growing interest in "quality" since the 1980s and suggested that the goal of what she called the "quality revolution" is to bring a "critical product to the customer that each time has consistent qualities." This requires robustness and reliability, and means using metrics to make it happen. "We are dedicated to protecting the health of the public," said Woodcock. "That is our goal."

She also spoke on having a company quality culture that allows employees to speak up when they see something wrong and that employees should not live "in a state of fear" when wanting to speak up. Her discussion of fear and a quality culture then turned to what she described as a "fundamental

*ISPE CEO John Bournas (left) and Merck & Co. Executive Vice President Willie A. Deese*

*Genentech Vice President Diane Haggerty (left) and Willie Deese*

*Acting director FDA/CDER/OPQ/OPP Ashley Boam*

issue" between the industry and the FDA – that is the fear that industry has of the agency. The FDA is not going to attempt to "nail" people, she promised.

"This is a huge problem; I'm not making this up about fear," she said, and referred to questions that had been raised around "what will the FDA do with the reports generated by using quality metrics?" She asked "How do we get to a better place where quality is not equated with a lot of inspections? How do we decrease inspections? By having a standardized and robust system of quantitative measures that we can trust. I don't want quality metrics to increase the fear factor."

Woodcock posed a fundamental question: "What is the state of pharmaceutical manufacturing in the US now?" She said that she doesn't know, but needs to find out. One problem, she noted, was that the industry is so spread out in terms of the varieties of products (generics, OTCs, CMOs), and also with non-US-based manufacturing sites about which FDA did not have adequate information. "Without standard measures we can't get to a system in which we have trust," she concluded.

## Overheard at the Workshops

*Peggy Speight, Executive Director, Bristol-Myers Squibb*
**Workshop 1: Data Submission: 21 April**

"How is data to be submitted?" was discussed in this workshop. According to Speight, participants focused on getting clear, crisp definitions that were "precise and harmonized." The value of this effort might provide a "return on investment" for those participating in the Quality Metrics program that might include a reduction in FDA inspections, suggested Speight. Other suggestions that came out of the workshop included having a training program for data submission, establishing grace and verification periods, and developing ways to ensure data confidentiality. Standardized templates would also help data submission, said participants.

*Brian Winship, Mylan*
**Workshop 2: ISPE Recommended Metric Set: 21 April**

Metrics for Critical Complaints Rate (CCR), Lot Acceptance Rate (LAR) and Deviations Rate (DR) were discussed in this workshop. "The meaning of 'critical' was debated," said Winship. "Also, comments about CR included debate about the numerator."

LAR needed a clear definition, said participants, and issues such as defining both "lot" and "rejections" provided spirited debate, particularly when it came to CMOs and cross-site steps. DR might not be a good indicator of product quality, suggested some participants. Discussions about major and minor deviations focused on definitions.

Other points discussed and debated in the full workshop included general questions about data collection. "This workshop provided good input for questions that can be taken up in Wave 2," said Winship.

## More Learnings from the ISPE Quality Metrics Pilot Program, Wave I

**Q What information from the metrics program will FDA be likely to consider using and how will the pilot influence the FDA going forward with their metrics program?**

A (*Russ Wesdyk, FDA*) Keep in mind that the information that FDA collects is limited to information that an investigator would already be asking for, something you have to have anyway. We want to minimize the burden, keep the definitions as simple as possible, and keep the footprint as minimal as possible. We are interested in getting the most "bang for the buck" without increasing the burden. With regard to question of which metrics the FDA might use, based on where we are that's something I can't speak to specifically. Will the ISPE metrics program influence the FDA? Yes. Will it directly impact the FDA? No. ISPE is not the only stakeholder.

**Q How will the ISPE Quality Metrics Pilot Program benefit companies that were not involved in Wave I?**

A (*Diane Hagerty, Genentech*) First, you are here! That's great! The report is going to be available to everyone, including regulators. Many things were learned in the case studies and what we learned will be considered in Wave II.

**Q Given the estimate that it took an average of 90 hours for participants to collect data, will there be a report addressing the ranges of how long it took for companies to collect the data?**

A (*Vanya Telpis, McKinsey*) We will work to provide information on the ranges.

**Q Please comment on the report data that says "Total Complaints" were difficult to provide.**

A (*Russ Wesdyk, FDA*) I don't get it. We would be interested in hearing from companies on why they were difficult to provide. I'd welcome any feedback on it. (Feedback from the floor suggested that while TCs are routinely collected, they may not be collected for all sites for the company, but may have been in the past collected for specific sites, a simpler task. Asking for the metrics with a new, specific definition may have required a different process for collection for some companies.)

**Q Across the supply chain there is no standard platform for the exchange of data, and that is a challenge to a robust quality system. This issue of IT structure might be the "elephant" in the room.**

A (*Diane Hagerty*) A point well taken. The issue of different platforms is getting the attention of senior management. It's not going to be easy moving forward, considering multinational companies, for example.

A (*Russ Wesdyk*) I'd like to comment on data systems and where data resides. An annual product review is a requirement. (Wesdyk conducted an informal, on-the-spot survey and asked the audience to self-identify if their company did not do an annual review across all sites and found that only 30 percent (estimated) of the audience did do an APR across all sites.) Everyone in your family takes drugs that you make, yet 60 percent do not aggregate an annual product review to understand at the corporate level what is happening with your product across the supply chain. Think about that.

### ISPE Quality Metrics Pilot Program

Diane Hagerty, offered a "time line and highlights" review of the ISPE Quality Metrics Pilot Program. She touched on everything from early informal discussions about metrics in 2013, to a 2013 "white paper" recommending a metrics pilot project, to the Brookings Institution meeting at FDA's request in May 2014, to the establishment of the Task Force in June 2014 and the engagement of McKinsey & Company as a third-party partner to receive data and ensure data confidentiality.


*"You Can't Improve What Can't Measure" plenary session (top); breakout sessons (middle and bottom)*

Hagerty also offered several points covered in the data summary, including information about the participants' data-collecting burden, which averaged 90 hours for participating companies, most of which were larger. The 90 hours of data collection, if done annually, could translate into a cost of $35 million, or more, said Hagerty. The metrics collected in the pilot study included an analysis of relationships between metrics across broad groups. She cautioned that the relationships they discovered were not necessarily causal.

Hagerty announced that Wave 2 of the ISPE Quality Metrics Pilot Program would start in June.

Telpis and Rutten, both with McKinsey & Company and on the metrics task force, offered analysis from the pilot's data and commented on the process of collecting it. Telpis was part of the "definitions sub-team" charged with providing precise definitions to aid data gathering. The sub-team spent considerable time in discussion with participating companies about definitions as the data collecting got underway, she said.

Rutten pointed out some of the relationships between data and discussed some of the emerging patterns and their implications. Not all of the relationship data between metrics was statistically significant (at 95 percent), but some relationships were. Some relationships were not surprising while others were, said Rutten. For example, critical complaints were a better reflection of quality than total complaints, he said. Sites with US recalls have higher deviation recurrence, and some metrics are more relevant to quality than others. "There is value in analyzing data in a protected environment," he concluded. "I learned a lot."

## GUIDANCE DOCUMENTS

### Forthcoming ISPE Guidance

The **ISPE Baseline® Guide: Science and Risk-Based Cleaning Process Development and Validation** is the newest publication in the series of ISPE Baseline Guides.

The Guide focuses on the cleaning of equipment product contact surfaces and addresses how well-established and accepted risk assessment methods can be used to develop health-based limits, such as Maximum Safe Carryover (MSC) values, based on ADE. It provides a new approach to meeting regulatory expectations for cleaning and a fresh perspective on cleaning and its validation using science, risk, and statistics.

The **ISPE Good Practice Guide: Operations Management** addresses all operations in the supply chain from the selection of raw materials to the distribution of drug products to customers and, ultimately, patients.

The Guide is a source of good practices covering a wide variety of themes, subjects, problems and issues faced across the realm of pharmaceutical operations. This guide is intended to provide industry professionals and stakeholders the opportunity to build and use a common language and a way to use generic and specific tools while acquiring a deep understanding of operations management processes and supporting technologies.

The **ISPE Handbook: Sustainability** is based on the premise that there is a viable path to the achievement of sustainability that responds to all precepts of the life-sciences industry. Key objectives include providing a global pharmaceutical sustainability baseline for the life-sciences industry through promoting consideration of the reduction of finite resources and environmental shifts along with promoting the development of sustainability policies and guidelines that apply to specific organizational needs.

The **ISPE Good Practice Guide: Decommissioning of Pharmaceutical Equipment and Facilities** is intended to be a 'one stop shop' for basic information required for the decommissioning of both equipment and facilities. Information is provided on best practices for the planning and execution of decommissioning and disposal of assets ranging from a single item to an entire facility.

**Revisions**

The third edition of the **ISPE Baseline® Guide: Oral Solid Dosage Forms** contains numerous updates and considerations, including expanded discussions related to Risk Management, Product and Processing, and containment and cross contamination issues.

An expedited revision of the **ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP)** is also underway in order to incorporate the recent EMA GMP updates related to cross-contamination and better align section topics with the ICH Q9 model.

**Other guidance documents in development** consider topic areas such as:

- Controlled Temperature Chamber Mapping
- Management of Engineering Guidance Documents
- Sampling for Pharmaceutical Water, Pharmaceutical Steam and Process Gases
- IT Infrastructure (Second Edition)
- Single-Use Technologies
- HVAC and Process Equipment Filters

## AFFILIATES

***This issue, our contributors report on events held in ISPE affiliates in Malaysia, Japan, China and Boston.***

### ISPE Malaysia

***GMP Conference 2015: Integrating World Knowledge Towards Regional Operational Excellence***
***by Rohani Mohammad***

This year's ISPE Malaysia GMP Conference was held early in the year in February at the Puri Pajangga Hotel, Universiti Kebangsaan Malaysia (UKM), with an experienced group of local and international speakers. The conference was a collaborative effort between ISPE Malaysia and the National Pharmaceutical Control Bureau (NPCB), Ministry of Health Malaysia. It was with great pleasure that the ISPE Executive Committee and the Conference Organizing Committee saw a record attendance from both members and non-members, firmly acknowledging the importance of ISPE in Malaysia. The participants comprised of industry professionals, academia and students from various local universities. The Ministry of Education sponsored academia and student participants.


*Participants at the ISPE Malaysia GMP Conference, February 2015*

**Welcoming address by Azhar Hussain, President, ISPE Malaysia**

ISPE Malaysian President, Azhar Hussain opened the two-day conference with a welcoming speech. This was followed by the opening address by Dato' Eisah A. Rahman, the Senior Director, Pharmaceutical Services Division, Ministry of Health Malaysia, who then proceeded to officially open the 1st ISPE Malaysia GMP Conference 2015.

The keynote speaker, the Director of the National Pharmaceutical Control Bureau (NPCB), Mr Tan Ann Ling provided the regulatory updates for the Malaysian pharmaceutical industry. This includes the updates concerning GMP and GDP issues in the Malaysian regulatory space, covering topics such as the Implementation of a Vaccine Lot Release System and the Enforcement of Cold Chain Monitoring in GDP Inspection. Both topics are considered 'hot' topics in Malaysia and the presentation was the highlight of the conference for many as it is rare to get such an opportunity to listen to the head of NPCB in person.

Many more informative sessions were held over the next two days with experienced

speakers sharing their knowledge and experiences in a wide range of topics including Engineering QBD, QC Lab Inspection, Biopharmaceutical API Manufacturing and Critical Utilities for the Pharmaceutical Industry.

Along with the official presentations there were also a couple of informal panel discussions with audience interaction discussing human capital requirements in Malaysia for the pharma and biopharma industries.

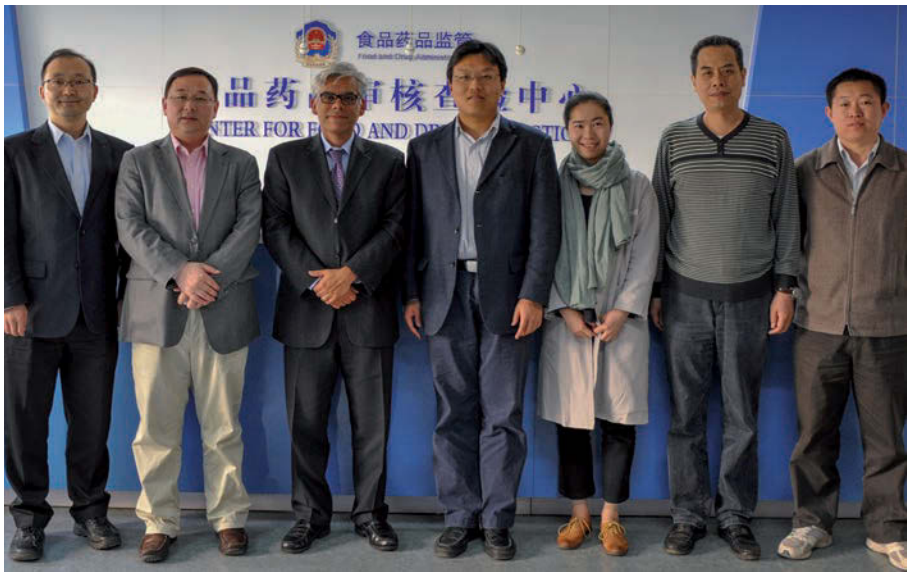
This was another great event held by the Malaysian ISPE Affiliate, bringing together a wealth of experience with regional speakers, more than willing to share their knowledge with the enthusiastic and questioning audience.

The Malaysian Affiliate is currently organizing further seminars and workshops for 2015, and look forward to working with current and future members.

ISPE Malaysia would like to thank all speakers, participants, sponsors, the Ministry of Education, the exhibitors and in particular the National Pharmaceutical Control Bureau (NPCB) for all their assistance with the program, speakers and conference set-up.

## ISPE Japan and ISPE China Affiliates welcome John Bournas to their Annual Conferences

ISPE Japan Affiliate held its annual conference in Tokyo from April 14 to 17 at the Tower Hall Funabori. In addition to meeting with the Affiliate's board members, ISPE President and CEO John Bournas delivered a presentation to conference participants.




*ISPE CEO John Bournas tours China's Center for Food and Drug Inspection in Beijing*

## ISPE CEO Attends China Annual Conference

Close to 700 industry leaders, regulators, and pharmaceutical professionals attended the ISPE China Annual Spring Conference from 20–21 April 2015 at the Westin Beijing Financial Street.

In advance of the conference proceedings, ISPE's President and Chief Executive Officer John Bournas toured the Center for Food and Drug Inspection (CFDI), an affiliated organization of the China Food and Drug Administration (CFDA), on 17 April. During the visit he met with the CFDI's Deputy Director General Jinglin Sun. The two exchanged ideas on how to enhance cooperation and support good manufacturing practice (GMP) implementation in China.

On 19 April, Bournas attended the Development and Future Trends on CMC (chemistry, manufacturing, and controls) Evaluation and GMP Inspection Forum, a preconference event organized by ISPE and the China Center for Food and Drug International Exchange (CFDIE), another CFDA affiliate. The event hosted more than

*Participants at the ISPE Japan Annual Conference in Tokyo, 14-17 April*

# ISPE Guidance Documents

## You Have Questions. We Have Answers.


**What you need to know and how to apply it.**

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ISPE's series of documents offer practical answers to the complex, dynamic challenges facing facility designers today by addressing GMP as well as non-GMP issues.

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*Bournas delivers the keynote speech at the ISPE China Annual Spring Conference*

70 keynote speakers and drew officials from the US Food and Drug Administration (FDA), the CFDA, and several of its branches: CFDI, the Center for Drug Evaluation (CDE), National Institute for Food and Drug Control (NIFDC), and ISPE Chinese Pharmacopoeial Commission (ChP) affiliates. Participants exchanged views on key issues about integrating CMC evaluation and GMP inspection for drug development and regulatory application.

Close to 700 participants attended Bournas's presentation of ISPE global initiatives, including the Drug Shortage and Quality Metrics Pilot Program. Bournas also delivered the keynote speech at the conference plenary session on 20 April and presented the China Honor Award to ISPE China volunteers. The 2016 Conference will be held in Shanghai.

## SEEKING INPUT AND CONTRIBUTORS FOR RISK-BASED APPROACHES TO SAMPLING FOR UTILITY SYSTEMS DOCUMENT

ISPE is seeking volunteers to develop an approach that can be used by industry to define a risk-based sampling strategy for a pharmaceutical water system. This group would come together to write a discussion paper to initiate debate and possibly lead to the creation of a guide.

While regulatory requirements identify the critical quality attributes of various grades of pharmaceutical water based on its intended use, these requirements do not specifically address sampling frequency or duration.

The general regulatory expectations found in various compendia are:

- USP General Chapter 1231 states that "water systems should be monitored at a frequency that is sufficient to ensure that the system is in control and continues to produce water of acceptable quality" and "the sampling plan should take into consideration the desired attributes of the water being sampled".
- EU Guidelines to GMP, Volume 4, Annex 1 states: "water sources, water treatment equipment, and treated water should be monitored regularly for chemical and biological contamination and, as appropriate for endotoxins".
- JP (XVI) Annex 2 states: "The frequency of measuring these parameters should be determined based on the stability of water quality." And "sampling frequency should be established based on validation data".
- ICH Q7, Section 4.20 states: "all utilities that could impact quality (e.g. steam, water, compressed air…, etc.), should be qualified and appropriately monitored and action should be taken when limits are exceeded".
- The FDA Guideline to the Inspection of High Purity Water Systems "recognizes that more than one approach [to sampling] may be acceptable," but that during the validation of a water for injection system, "the samples should be taken daily from a minimum of one use point, with all points of use tested weekly". This guideline does not specify sampling frequency once the system has gone through a 12-month validation period.
- PDA Technical Report TR-13 reports specific guidance for sampling frequency which appears to be extrapolated from the above FDA guideline, stating that for water for injection systems: "rotate testing of all use points weekly for micro, test return loop daily for chemistry and endotoxin".

With the widespread adoption of risk-based approaches in the pharmaceutical industry, it makes scientific sense to review and, if justified, challenge the necessity of sampling every use point in a water system on a weekly basis.

This potential paper would suggest some initial guidelines for utilizing risk assessment tools to determine if sampling frequencies can be reduced without impacting product quality or patient safety while saving pharmaceutical companies significant amounts of time and money through reduced sampling.

With a lack of regulatory guidance regarding sampling frequency, industry has adopted sampling practices that typically follow the sampling frequency mentioned in the PDA TR-13 guidance: sample all system use points in a water-for-injection system such that each point is sampled at least once in a working week, with a daily sampling of the distribution loop return.

The current version of the USP proposes adoption of a risk-based approach – without describing what that might be. The major risk would be the potential for water from the system to impact the quality of the finished product. Risks to patient safety are very difficult to quantify, as there are too many potential variables; whereas the risk to impact the final drug quality is easier to determine.

Factors to be considered include:

- What is the water used for? What other processing stages are there?
- Water supplied for rinsing a vessel used for a solvent-based reaction in the creation of an oral solid dose medication has very little potential to create a risk to the final product quality, whereas water used for the final wash of a RABS for a filling machine used for sterile drug processing is far more critical.
- Can we consider the water to be in one of the following three "severity" categories aligned to the potential risk of impacting finished product quality?

If you believe you have expertise to offer, we welcome your input and encourage you to get involved by taking the survey by 31July 2015 at https://ispe.co1.qualtrics.com/SE/?SID=SV_3qhVV1ob64eUar3

## APPOINTMENTS

**Maria Robertson**, Senior Director, Marketing Communications

Maria Robertson joins ISPE as Senior Director, Marketing Communications, reporting to Shane Osborne, Vice President, Membership and Marketing Communications.

Maria is a highly skilled professional with 20 years of experience in association marketing. Prior to ISPE, Maria led the Communications Department at the School Nutrition Association (SNA) with oversight responsibility for the development and delivery of numerous communications strategies, policies and products, including SNA's website, conference promotional materials and magazine. One of her most recent accomplishments included a full redesign of the SNA website (launched in July 2014). Maria was recognized for this redesign with a MARCOM Gold award. Maria has participated in association strategic planning, policy and technology decisions and has had direct responsibility for generating $2 million in magazine and website advertising each year. She holds a Bachelor's degree in Communications from James Madison University and is a member of the American Society of Association Executives (ASAE) and Association Media & Publishing.

**Meredith Ellison**, Director, Continuing Education

Meredith Ellison joins ISPE as Director, Continuing Education, reporting to Susan Krys, Vice President, Product Development.

Meredith is a seasoned association professional with over 15 years' experience in educational event life-cycle from inception to execution. Prior to Young Presidents' Organization, she was Director, Program Development, for the Advanced Medical Technology Association (AdvaMed) and worked for several other associations including RAPS. Meredith holds an MBA from the University of Maryland, University College, is a member of the American Society of Association Executives (ASAE) Professional Development Council and holds a Certified Association Executive (CAE) certification from the ASAE.

**Amy Loerch**, Manager, Publications (Guidance Documents)

Amy Loerch joins ISPE as Manager, Publications (Guidance Documents), reporting to Anna Maria di Giorgio, Senior Director, Global Communications.

Amy has over 30 years' experience as a professional writer, editor, and researcher. Before joining ISPE, she was a senior consultant at the strategy and technology firm Booz Allen Hamilton, where she produced a magazine for the military's Central Command and developed training materials for the civil health market.

Previous positions included serving as publications manager for an ophthalmic biopharmaceuticals firm in Tampa, a copywriter at two marketing and advertising agencies, and the owner of a freelance writing and editing business. Amy holds a BA degree in English literature from Western Connecticut State University.

## CALL FOR ARTICLES

If you are a subject matter expert in the global pharmaceutical industry with knowledge of the latest scientific and technical developments, regulatory initiatives or innovative solutions to real life problems and challenges, *Pharmaceutical Engineering* wants to hear from you.

We are seeking articles with a global perspective for 2015 with an editorial focus on risk in the pharmaceutical industry.

**September/October 2015**
***Risks Associated with Product Performance:***
Specific topics could include: risks and absence of bio relevance, patient compliance, product compatibility and in-use and devices.
**Manuscripts: 18 May 2015**
**Publishes: 21 September 2015**

**November/December 2015**
***Risk-Based Regulatory Review:***
Specific topics could include: benefit vs. risk, clinically relevant specifications, comprehensive control strategy, regulatory commitments and post-approval change management protocols.
**Manuscripts: 9 July 2015**
**Publishes: 23 November 2015**

### How to Submit an Article for Review

Application articles and case studies will be considered for a variety of new departments, including facilities and equipment, information systems, product development, production systems, quality systems, research and development, supply chain management, and regulatory compliance. In addition, we are looking for special features and guest editorials that focus on new technology, contemporary quality management practices and production innovation. For more information, please visit *Pharmaceutical Engineering* website and click on Submit Article.

If you have any questions or would like to recommend a topic for this issue, please email lgoldbach@ispe.org.

We look forward to counting you as one of our distinguished *Pharmaceutical Engineering* authors!

# ISPE DEVELOPING GAP ANALYSIS TOOL TO HELP ENSURE UNINTERRUPTED SUPPLY OF MEDICINES

## Tool to aid manufacturers locate gaps in production and quality systems

**Pharmaceutical manufacturers will soon have additional means with which to address the global issue of drug shortages.** ISPE unveiled plans for a new tool to locate potential gaps in production and quality systems, the Drug Shortages Prevention Gap Analysis Tool (Gap Analysis Tool), on 6 May 2015 at its Annual European Conference in Frankfurt, Germany. Under development by ISPE's Drug Shortages Task Team, the new tool promises to be an important advancement in the effort to prevent drug shortages around the world.

"The Gap Analysis Tool will provide manufacturers across the spectrum of the bio/pharmaceutical industry with methods to locate current and future inconsistencies across the pharmaceutical manufacturing supply chain," stated ISPE President and CEO, John Bournas.

During the Gap Analysis Tool's public debut in Frankfurt, task team members emphasized it is meant to be a change process tool to be used to highlight any area of a quality system where there is potential for non-compliance. Public reaction was positive, said Bryan Wright, ISPE's European Regulatory Advisor. Feedback received from conference attendees will be used to refine the Gap Analysis Tool so that it is as effective and applicable as possible for helping to prevent global pharmaceutical manufacturing non-compliances possibly resulting in product quality issues and resulting supply chain gaps identified with causing drug shortages and affecting patients worldwide.

### Rooted in data

The drug shortages survey ISPE conducted in 2013 demonstrated that the root causes and reasons behind drug shortages could be found everywhere and anywhere in the supply chain: rom starting materials or at any point up or down the supply stream. Input from industry and regulatory stakeholders regarding the ISPE Drug Shortages Prevention Plan (DSPP) released last year resulted in a consensus around the need to develop a tool that will enable industry to implement some of DSPP's recommendations.

ISPE's vision was to create an easy-to-use guide for use by corporations to identify gaps in culture, quality, capabilities, business continuity, and associated systems that, when applied, should reduce the likelihood of drug shortages. The guide, applicable in the United States, the European Union and worldwide countries, effectively builds on the previously published ISPE drug shortages documents discussed below. The Gap Analysis Tool is unique in that it can simultaneously serve as a valuable reference to industry to self-identify the gaps and build appropriate action plan as part of companies' overall drug shortages prevention programs, and to regulators to assess the existence and robustness of such prevention programs to avoid shortages of much needed medicines for patients.

The development of the Gap Analysis Tool is part of the third phase of ISPE's drug shortages initiative. Phases one and two produced the 2013 drug shortages survey, which focused on manufacturing and quality-related causes of drug shortages, and the development of the DSPP. The working foundation for the Gap Analysis Tool is the DSPP framework and its six dimensions: corporate culture, robust quality systems, metrics, business continuity planning, communication with health authorities, and building capability.

> ▶ The effort to reduce and eliminate drug shortages worldwide has come a long way since November 2012 when the European Medicines Association (EMA) first published a reflection paper that provided not only a framework for drug shortage assessment, but also advocated for an effort to raise public awareness of the drug shortage problem. ◀
>
> *François Sallans*

### A four-step process

The task team, led by François Sallans, Vice President and Chief Quality Officer, Johnson & Johnson, placed special emphasis on two dimensions: robust quality system and metrics. That emphasis advocates awareness, action and advancement. It also assists manufacturers with preparedness assessment and gap analysis tools, using a four-step process.

Step 1, is about commitment. "Today, the industry is accountable for drug shortage prevention," explained Sallans. "Drug shortages have direct impact on patients and also have socio-economic consequences. There must be a corporate commitment to preventing shortages, one that is embedded in a quality corporate culture."

Step 2, is to conduct a risk-based vulnerability assessment, using the Gap Analysis Tool under development. Step 3 focuses on remediation and will likely require a multidisciplinary team and development of site-specific or corporate-wide plans for using risk-assessment gap analysis and DSPP. This is a step that will benefit the overall site quality system. Step 4 entails implementing training, periodic review, ensuring continuity of product supply and, most importantly, maintaining a patient focus. The elements in Step 4 should be the cornerstone of a quality corporate culture aimed at preventing shortages.

Bournas is looking forward to the completion and release of the Gap Analysis Tool. "Manufacturers will be able to mitigate problems before they arise, allowing them to provide an uninterrupted supply of safe, quality medicines to patients worldwide."

For more information about the ISPE Drug Shortages Prevention Plan, please visit www.ISPE.org/Drug-Shortages-Initiative.

# MANAGING THE DESIGN OF A SINGLE-USE FACILITY FOR BIOMANUFACTURING

## Lessons Outside the Traditional Project Management Box

*Jeff Odum, CPIP*

**This article will identify many key design issues of an SUS and provide experienced-based guidance on how to address them.**

**It is a technology that holds the potential to revolutionize biomanufacturing as thoroughly as Apple® changed computing with its modular, out-of-the-box components.** And, like the popularization of desktop publishing this new technology holds the potential to democratize biopharmaceutical engineering.

Single-use systems (SUS) and products, and the modular design of manufacturing facilities, can benefit the biopharmaceutical industry by providing an alternative to traditional stainless steel tank setups that is innovative, flexible, portable, and cost-effective. In current processes for monoclonal antibody production, for example, the downstream processes – such as chromatography or purification – require a lot of buffers. Each buffer tank needs to be cleaned, sterilized and validated. If, however, buffers pre-weighed and single-use bags are purchased, facilities can save on their annual operating costs. Whether a company implements single-use technology across the board or just for media and buffer components, the design of an SUS is critical to success.

The transition to this new way of biomanufacturing is dependent on having an understanding of the critical physical and cultural implications of SUS implementation. While facilities already have the existing knowledge, experience and expertise developed from their stainless-steel stirred tank applications, and while vendors and suppliers can provide some of the needed information, partnering with SUS specialists to get reliable information and support about design and management is essential to get the best system, while avoiding cost overruns and delays.

### The Decision to Move to an SUS

The decision to introduce single-use technology into a biomanufacturing process is typically done for many reasons, including:

- Innovation
- Flexibility – the modular design can be adapted to new processes or replicated in many locations
- Cost
- Schedule
- Fixing a problem
- Product origination in clinical scale
- Reduction of cross-contamination
- Simplification of cleaning and cleaning validation
- Protection of workers from hazardous materials due to closed systems

Once the significant engineering design effort begins and the project manager and design team become involved to execute the project, there has typically been a commitment to the reason(s) that will drive the project and some level of project cost and schedule have been developed. Though this is often not the case in today's climate, it is preferred that these reasons be well documented and understood by all of the project sponsors and team and that they have been "cast in stone" so they become irrelevant in terms of project execution.

Many manufacturers have challenges launching an SUS project, in part because it is not the normal baseline on which the corporate experience is based. What is viewed as a potential solution might not be as clear-cut as first thought. Problems can be as simple as the design of a bioreactor bag, since each company provides unique bags. The portals that enter the bag might be particular and not work from one bag manufacturer to another. Product and process decisions need to be made early and are not as simple or as straightforward as they are for stainless-steel platforms, which have global standardization.

The transition to an SUS requires questions to be asked and decisions made regarding project execution that are outside the usual well-understood project management box:

- What are the technical challenges? (Can it even be done?)
- Will it really cost less?
- Can we qualify the systems to align with our regulatory culture?
- How many materials of construction will there be?
- How will vendors support our demands?
- Will our EHS group approve of how the systems will be used?
- Will our facility be "right sized" to handle this?

Therefore, the project manager might believe that moving to an SUS platform requires a leap of faith. Who will answer the outstanding questions from the request for proposal (RFP) from the internal or external customer? How will all of these opposing forces and process discovery affect the project budget and schedule? Managing this uncertainty within the scope of work can be viewed as chaos outside the known project management box.

The good news is that many of these questions from the RFP can be addressed immediately. Much of the project manager's job will be to reduce the uncertainty of embarking on a new way of manufacturing, but they need not do it alone. To make this a reality in today's SUS project evolution and implementation requires good support from the internal team, vendors, and outside consultants.

## Step-by-Step Guidelines for Managing the Design of an SUS Facility

Companies with traditional stainless-steel platforms have familiar standard procedures, methodology and technology. The same topics of design, product choice and risk assessment are present with an SUS, but they will not be addressed in the same manner. It is important from a product management standpoint to understand what these are, ensure the necessary attributes are identified and involve the right people to make decisions. For example, you might discover during implementation that a particular fitting from a vendor is not compatible with your other equipment. For many companies, this is work they are not aware of, and big problems can arise when little nuances are not addressed.

### *Step 1: Identify Knowns and Unknowns*

The first critical step is to define the programming requirements into knowns and unknowns. The list of knowns at the outset of a project will be typical of other biomanufacturing systems. These include location, phasing approach, production scale and the process as defined by block flow diagrams. However, the unknowns require clarification of assumptions and identification of gaps in the project definition. These unknowns include:

- Process material balance: This is an unknown because it's not necessarily defined. A good example occurs when you transition from clinical production to develop a commercial manufacturing process. The throughputs will be different. It could be that, to meet the demands of the process, you need ten 500 L bioreactors instead of one 5,000 L bioreactor.
- Multi-product/phase approach: Manufacturers transitioning to an SUS are looking to produce more than one product. Each product could require a different approach.
- Final equipment vendors
- Biosafety considerations
- Staff capabilities and roles
- User requirements
- Raw materials
- Storage requirements

Sharing this list of unknowns allows the customer to assist in identifying gaps and be aware of the level of effort that will be needed to address them. A large portion of the needed information will come from external resources (e.g., SUS vendors and consultants) who should be brought into the project early in the design process.

Assumptions about the process might be used as a relief valve for organizations whose procedures are not flexible enough to drive early decisions. In these early stages, such assumptions might sound good, but as you move into developing the process design they become a crutch, preventing you from facing the inevitable. For example, a manufacturer might assume that the largest bioreactor they will use will be 2,000 L. Later, you might find out that EHS has a problem moving such a large bioreactor in a small space. What worked for manufacturing didn't work for EHS. Reducing the pressure by making these assumptions often leads to delaying significant decisions to a point in the project when surprises can have a large negative impact. While SUS facility projects may be able to proceed without having unknowns fully addressed, equipment-specific projects may need to address many of these unknowns first.

There has to be agreement on outputs and deliverables through all stages of the project design effort. The basis of design (BOD) and user requirements specifications (URS) become early deliverables. The URS development will require an extensive body of knowledge from a number of groups: manufacturing, engineering, vendors and quality. The expertise of these groups may benefit from input from outside the traditional resource pool such as external consultants.

Manufacturers rely on outside experts – consultants, vendors, and suppliers – not only for process design, but when new issues arise down the line. Keep in mind that planning for such contingencies helps because, once an outside support has finished its work, it can be difficult to re-engage them once these new challenges arise.

### *Step 2: Consider Product Characteristics*

While the process is paramount for SUS-based facilities – as it is for traditional stainless-steel stirred tank facilities – the issues become different.

Product characteristics must be defined and addressed at the start, particularly as they pertain to the potential for leachable and extractable constituents from the SUS products to contaminate the biopharmaceuticals being produced. This holds for bags, tubing, connectors and equipment components. Usually, unit operations equipment comes from multiple vendors, which means that integration of multiple SUS components needs to be addressed.

Unlike stainless steel, which has global standards about composition, single-use products are composites of many materials without universal standards. However, there are studies that have addressed issues concerning extractables and leachables so manufacturers can consider whether a bag film is compatible with the substance they are manufacturing. Keep in mind that bags from one company may be incompatible with the fittings supplied by a different vendor. Biomanufacturers can work with bag manufacturers to ensure their chemical process functions properly with each bag. A good consultant can help you with bioreactor and bag design; make sure your line sizings are correct, and that the number and position of connections is accurate.

***Step 3: Determine the Critical Parameters of Your SUS Operation***

The design process takes into consideration parameters such as scale, temperature requirements, flow rates from one part of the process to the next, bag, tube set, and connector characteristics, and defining what the unit operations are.

Scale is of interest because one of the main benefits of single-use technology is the ease and relatively low cost of scaling up, which can be accomplished merely by incorporating larger tanks. Some companies with little experience scaling up an SUS from R&D to production look to clinical manufacturing operations for guidance. However, scale-up from clinical to commercial manufacturing does not have the same attributes and operating parameters that form the baseline for previous experience with stainless-steel, stirred tank platforms. There are limitations on what is commercially available and of the portability of some larger-scale SUS components. Decisions on whether to scale up or scale out should be addressed early.

The resulting process may become a hybrid, where both SUS and traditional systems are combined.

***Step 4: Identify and Mitigate Risk***

Risk management is necessary for all biopharmaceutical platforms. Once the product characteristics and process parameters are understood, the design team needs to identify and understand risk elements for each part of the SUS production chain. Two of these that we'll look at are closure analysis and supply chain management.

*Closure Analysis*

For each division of the manufacturing process, risk mitigation confirms that the SUS operates in a closed manner that can be validated. First, the closed system is separated into three parts:

- Equipment assembly: bioreactors, vessels, filtration systems and chromatography systems
- Streams into and out of the system: compressed air, exhaust, media, and buffers
- Connections and disconnections to the system: valves, double-block, valve-ring, single-use connectors and disconnectors

# Production downtime is not an option

## In the new pharma reality you need to implement changes on a regular basis – without causing production downtime

In the new pharma reality, changing production demands create a constant pressure for changes to processes and facilities. At the same time, maintaining the production throughput requires that production downtime is minimised. Upgrading a facility with minimal shutdown time is thus an essential ability for achieving success. NNE Pharmaplan has expertise in handling projects in fully operating plants and can help you turn your old facilities into future business assets. We provide meticulous planning and experienced project teams who know and understand the challenges of reestablishing a fully GMP-compliant production after each shutdown.

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Second, the definition of "closed" must be agreed on for each part of the process by the entire team, as closure is not a constant. Here are three of the most common definitions of a closed system:

- Closed system is one that is designed and operated so that the product is isolated and never exposed to the environment. Additions to, and effluents from, closed systems must be performed in a completely closed fashion. Transfers into or from these systems must be validated as closed.
- Functionally closed systems are opened between processing operations but are rendered closed by a cleaning, sanitization, or sterilization process that is appropriate or consistent with the process requirements, whether sterile, aseptic or low bio-burden.
- Briefly exposed operations: Open processes containing process materials and/or product intermediates. These open processes are rendered closed by means of an appropriate closing process. Definition and validation of the pre-closure incubation phase is critical.

Once closure has been defined, it becomes the task of the design team to execute a process closure analysis. This is straightforward with a stainless-steel system because it has been done many times before. And while closure is not unique to single-use systems, how to address it for each part, is. Therefore, risk analysis is performed for each connection, for the design of single-use components, and to ensure operators of an SUS are properly trained. A good example would be a tube set that has been purchased from a vendor. It has multiple connections to a bioreactor and each has to be connected properly and verified. Each connection might have a different risk, making risk analysis time consuming because the data used to assess this is new.

Figure 3 shows a three-phase approach that can yield excellent results and meets current regulatory guidance for overall risk identification and analysis.

*Supply Chain Management*

Supply chain management of an SUS-based biomanufacturing project requires the following to be addressed:

- Compatibility of materials
- Quality and testing standard and criteria
- Delivery
- Redundancy in the supply chain

Tube set management is an important aspect of the supply chain that warrants a more detailed discussion.

*Tube Set Management*

Many of the complexities of SUS facility design have their roots in tube set design, management and quality control. The previous discussion of closure analysis also applies to tube sets. Material compatibility of tubing, fittings, devices and bags is critical. For assembly, whether tube sets are manufactured in-house or supplied by a third party impacts inventory management and personnel training.

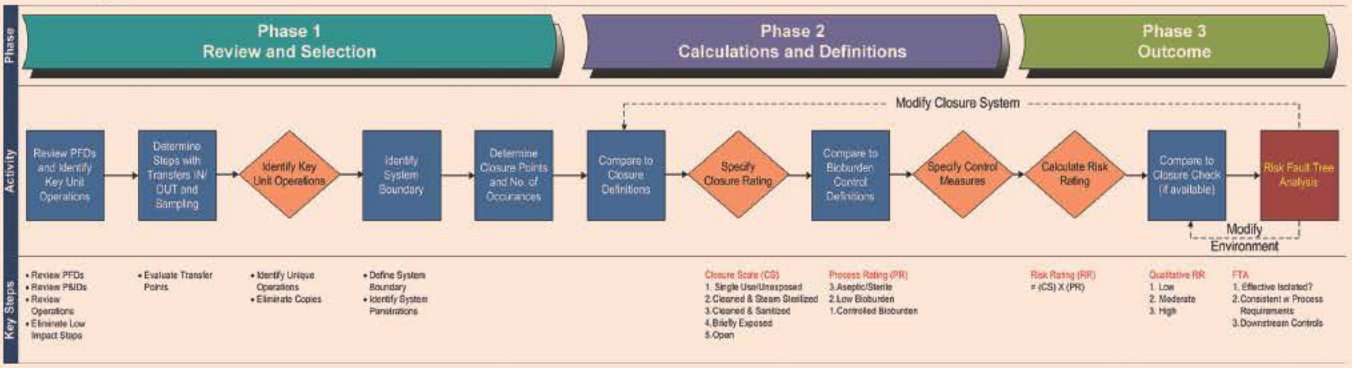
Tube sets can be complex, integrated assemblies in which the design is critical to closure validation and process operation. The assembly, packaging, inspection, and disposal of the large number of units required to operate an SUS has to be well defined in the facility's process design. New procedures will be required to analyze these activities. The training of personnel in the use of these components will also be a focus for risk mitigation.

***Step 5: Ensure Design Is Flexible and Adaptable***

Designing an SUS to be flexible and adaptable for future manufacturing opportunities and scenarios makes good business sense. What does flexible mean in terms of design?

Flexibility can focus on the multi-stage goal of manufacturing from a single facility asset. From early stage clinical manufacturing through launch and commercial manufacturing, the facility has

**Figure 3** Single Closure Analysis Activities




Source: BioPhorum Working Group

Figure 4 Single-use Tube Set Drawing

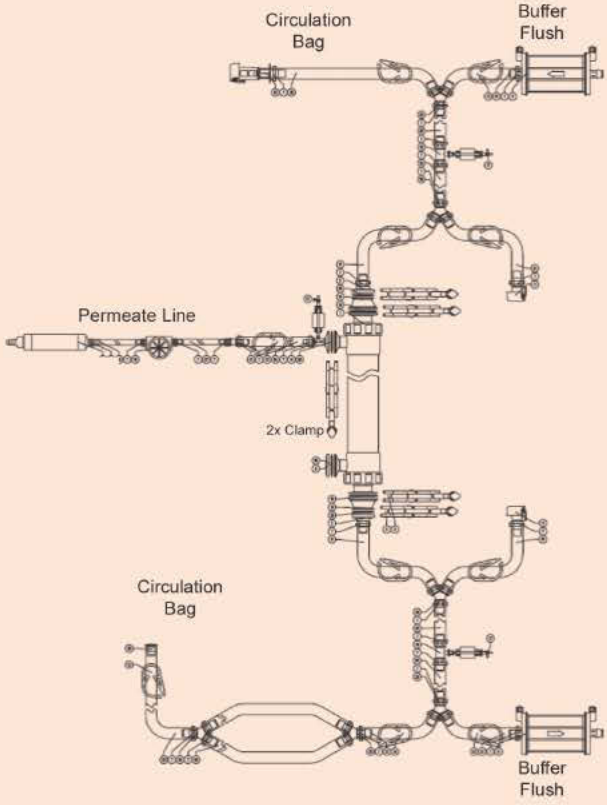



Figure 5 Facility Types

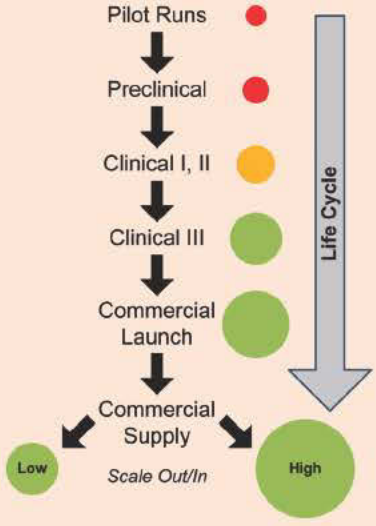
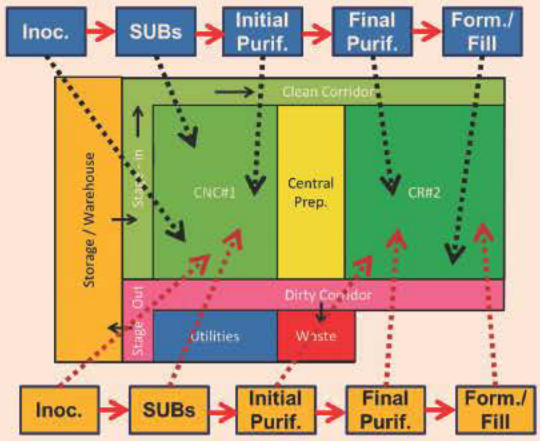
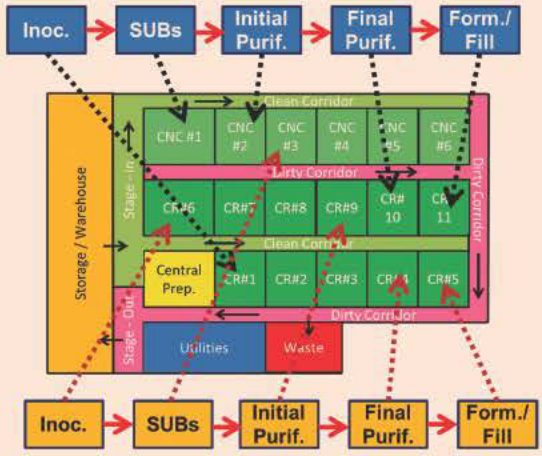



Figure 6 Ballroom Manufacturing




Courtesy of IPS

Figure 7 Matrix manufacturing concept




Courtesy of IPS

to be designed in a manner to allow for a flexible segregation strategy, multiple manufacturing platforms and a likely increase in scale.

To accomplish this goal, organizations are developing manufacturing configurations around the "ballroom" concept; the "matrix" approach of highly segregated, yet flexible, manufacturing suites;

or a hybrid solution with elements of both. Any of these options requires synergy between the process unit operations, operational philosophy, segregation approach and design attributes.

Once the facility design parameters are defined, the delivery approach and its impact on the design attributes can be addressed. Today, many SUS facilities are taking advantage of different modular-based delivery approaches: modular cleanroom panel assemblies, modular units, rapid deployment pods, and the traditional "stick-built" delivery are all viable options that have different design requirements for infrastructure, tie-ins, accessibility, redundancy and space flexibility.

## The Path Forward

Designing an SUS project for the new realities of the biopharmaceutical industry is a novel process and different from past experience. It might be that the perspective of an existing operational history will be of limited use. Understanding and accepting the drivers of the project is critical. Process attributes and critical process parameters will be different, the risks will be different and there will be new focus on the supply chain.

While there is no need to panic, it is important to understand where the risks lie, how to address their potential impact on the project and manage the design accordingly. Any new data from clinical studies and process development is valuable, for both the good and the bad. Figuring out early what is unknown, asking lots of questions and not settling for vague or incomplete answers will help keep the design process on time and on budget.

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## About the Author

**Jeff Odum, CPIP** is a globally recognized SME in biomanufacturing facility design and compliance. With over 25 years of experience in design, construction, compliance and operations, he has managed over $2.5 billion in capital projects and has published over 100 technical articles on these and other key industry subjects. As a Certified Pharmaceutical Industry Professional (CPIP), he has led numerous professional training and development courses across the globe and is a member of the ISPE technical training staff teaching courses in facility design, project management, process design, and compliance. He also is a Teaching Fellow in the Biomanufacturing Graduate program at North Carolina State University's Bioprocess Training and Education Center (BTEC) and has been an invited lecturer and presenter at over 100 academic and global industry programs.

## YOUNG PROFESSIONALS

# Benefits of Being Part of the ISPE Casa Chapter and Philippines Affiliate

*Remil Aguda, ISPE Philippines Affiliate*

**After working in the biopharmaceutical industry as a Process Development Engineer for almost five years and serving as a young professional member in the ISPE CaSA chapter from 2008–2012 and Philippine Affiliate since 2012,** I recognize that we always keep learning new tools, expanding our knowledge base and eventually lead events to create new tools, knowledge and professional connections.

Both CaSA and Filipino groups have provided ISPE career coaching events, vendor shows and technical seminars for latest technologies, and baseline guides. After college, ISPE was where I made connections which were beneficial to me when deciding where to begin seeking entry-level jobs upon graduation.

During the CaSA chapter technical seminars and social events, I interacted with professionals from suppliers, process development groups, manufacturing, technical support and even start-up companies. I was able to meet professionals representing an organization and joined them during meal breaks and social events. In my career, I found myself being surrounded by students, fellow professionals, both young and seasoned, and leaders in the biopharmaceutical field in the USA and Philippines.

I have met several engineers who shared the same interests in continuous professional development. Some of them were able to use a combination of the online graduate education and on-the-field engineering experience as exemplars in obtaining the certifications offered by ISPE.

With limited time and budget to go to school part-time, I found several free online short-term classes offered by reputable engineering universities and ISPE webinars helpful. They complement each other to cover fundamental knowledge and experience from the communities of practice, respectively. In my career in the US, my mentors sent me to 3–7 day programs offered in my local university and apply what I learned to complete our on-going biopharmaceutical process development projects.

These short week-long and day-long programs allowed me to increase my working knowledge in biopharmaceutical process development, project management, and biochemical analysis techniques. This exposure gave me great experiences and ideas to share to other members upon returning to my home country, the Philippines, and maintain my active membership in ISPE as part of the Philippines affiliate.

Upon joining the Philippine affiliate, I was able to share these learning paradigms to fellow colleagues in the pharmacy school in our national university, know the experiences in pharmaceutical facility design of business owners in the Philippines, and expand my knowledge base in Philippine pharmaceutical operations and regulations in contrast to their US counterparts.

When I was elected as a board member, I initiated the first career-coaching workshop patterned after the similar events we organized as a young professional committee for the ISPE CaSA student and young professional members. In this workshop for graduating college students, pharmaceutical leaders talked about their career paths, critiqued resumes and lectured about future needs in the pharmaceutical industry.

What do I foresee in the pharmaceutical industry in the United States and Philippines? Ongoing training of fresh college graduates and seasoned professionals would be key to sustaining an industry that supplies medicines around the world. ISPE can facilitate training as a global volunteer professional organization since pharmaceutical engineering is part of a college curriculum and as part of human resource development in any private or public entity. ISPE is in the best position to offer its expertise in this area through student career coaching workshops, plant visits of students in manufacturing facilities, day-long training on university campuses and industrial parks, and online access to technical baseline guides and webinars on its website. ISPE can be tapped to create pilot plant facilities shared by degree-seeking students, government regulatory agencies and industrial research scientists. Lastly, ISPE Baseline® Guides and technical workshops are venues for the ongoing harmonization of regulations in the Association of Southeast Asian Nations (ASEAN) region to comply with US and European regulations.

As I look back on my involvement in the ISPE groups in these countries, I am glad to be part of ISPE as a global organization that supports the growing demands for acquiring skills for young professionals in this complex and interdisciplinary world of pharmaceutical engineering.

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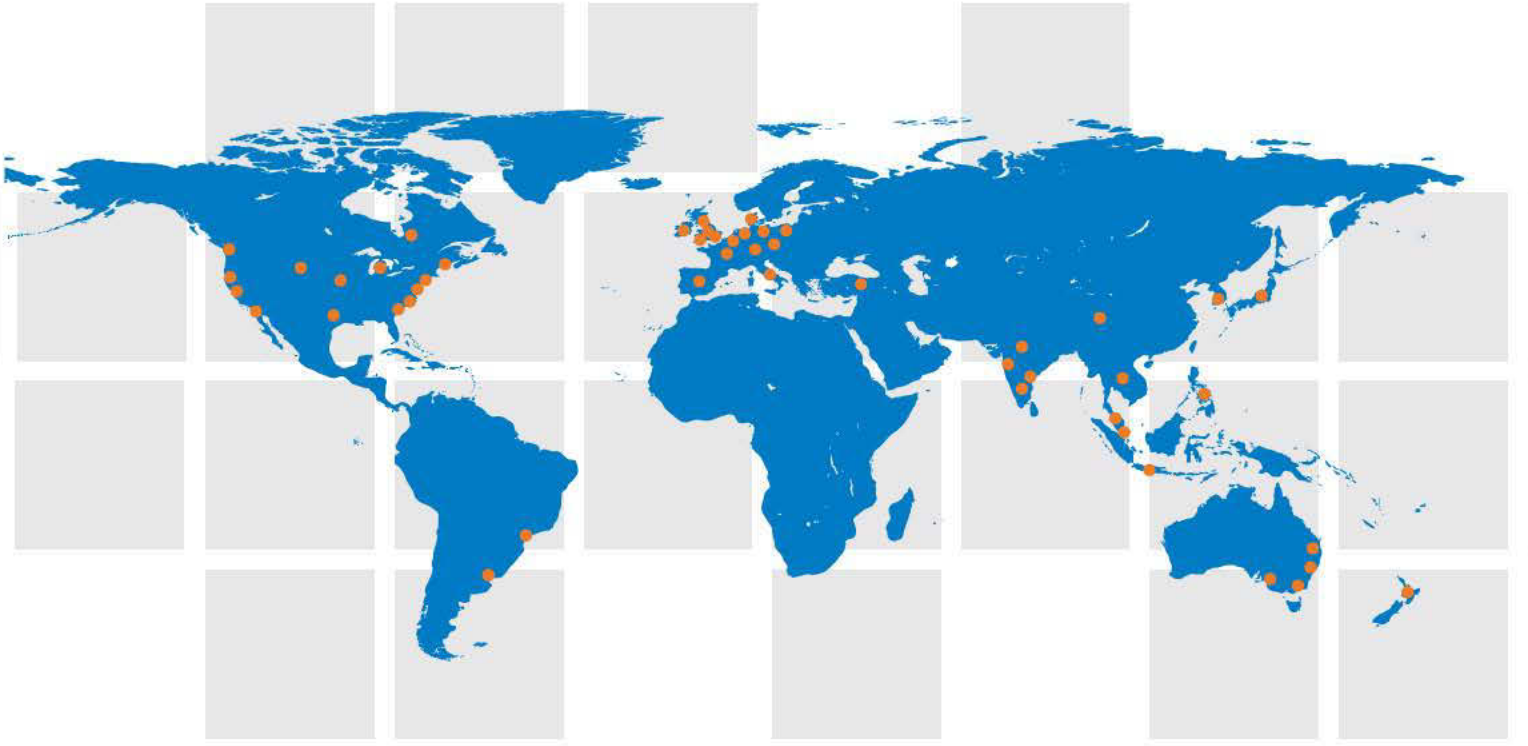

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# TESTS ON ROUGING AND EXPERIENCES DEALING WITH ROUGING IN PHARMACEUTICAL PRODUCTION

*Thomas Blitz, Ernst Felber, Robert Haas, Birgit Lorsbach, Andreas Marjoram, Roland Merkofer, Tobias Mueller, Nathalie Schuleit, Marc Vernier and Thomas Wellauer*

**Part 2 of this article describes tests and practical experiences in rouging formation and the influence of rouge coatings on cleaning efficiency.**

**Abstract**

*The present technical article (in 3 parts) discusses the current body of knowledge on the subject of rouging. It is based on insights from tests and operating experiences of companies that manufacture pharmaceutical medicinal products.*

*By means of a generic risk-based approach and a test setup derived from this, it is shown that the danger resulting from rouging for products and patients may be regarded as slight. As regards products, however, a conclusive appraisal may be obtained only by means of specific risk analyses. The risks resulting from derouging actions must also be considered in the overall assessment.*

*Part 1 of this article described the background on rouging, rouging formation, derouging and a risk overview.*

## Tests and Practical Experiences

The procedure for corrosion investigations is described in DIN 50905 Parts 1-5. The most important principles for conducting material compatibility tests are explained here.

During the investigations, the conditions for the various investigation parameters must be accurately defined and complied with. First it must be ensured that the correct material with the desired surface quality is available. Then the test conditions such as temperature, pressure and composition of the test medium must be defined and a suitable test apparatus selected.

During the course of the test, which usually lasts at least 4 weeks, it must be ensured that the parameters do not stray above or below the values fixed for them. An appropriate instrumentation and control system is required for this purpose. After the tests, an exact gravimetric and optical evaluation of the samples is usually made. For this purpose, a suitable analytical balance and a microscope must be available.

The limit value for technical resistance corresponds to a material removal rate of < 0.1 mm/a (millimeters per year). The requirements for pharmaceuticals or food products may be more stringent, however, since product contamination by heavy metals must also be prevented in these cases. The difficulty of the rouging investigation is that, even after long test periods (several months), it has usually been impossible to simulate the surface changes in the laboratory test. Furthermore, no significant material removal rates were measurable.

### Occurrence of Rouging Under the Effect of Clean Steam

To investigate rouge formation in clean steam systems, electropolished test plates of materials 1.4435, 1.4539 and 1.4571 were introduced into a clean steam system (138°C, 2.5 bar gauge). The weight variation was recorded as a function of time in order to determine a material-specific corrosion rate.

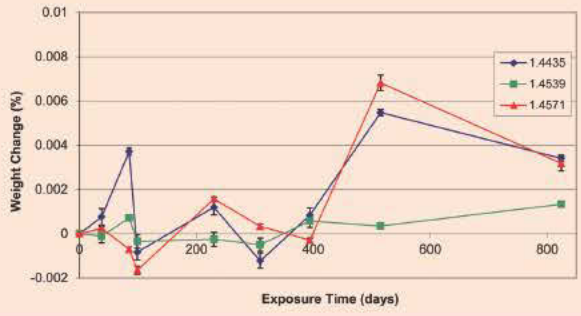
After an uninterrupted exposure time of 824 days, the test plates exhibited non-uniformly formed black, partly brownish discolorations (Figure 1). These discolorations exhibited only slight similarities to the rouge coatings observed on media-contacted surfaces of clean steam systems after prolonged operating times.

Because of the very small and unsteady weight changes of the test plates, it was not possible to determine the corrosion rates. Instead, the variation of the weight change over the test time was reported (Figure 2). A comparatively high corrosion rate of $3.4 \times 10^{-3}$ mm/a, as has been determined for WFI systems (at 85°C),[9] could not be confirmed for the investigated materials in a clean steam system.

**Figure 1** Test plates after an exposure time of 824 days


(a) material 1.4571 (b) material 1.4435 (c) material 1.4539

**Figure 2** Graph of the weight change of the test plates exposed to clean steam



**Influence of Hot Sodium Hydroxide Solution on Stainless Steel Surfaces**

The materials 1.4404, 1.4435, 1.4539, 1.4591, 2.4600 and 2.4602 were investigated as regards their behavior toward hot sodium hydroxide solution.

Electropolished test plates of the materials were exposed continuously to sodium hydroxide solution (1% NaOH; temperature ≥ 78°C). The material-specific corrosion rates were determined by weighing the test plates at regular intervals to measure their change in weight. Moreover, the surface conditions were visually appraised and the surface topographies and compositions were analyzed by means of SEM and ESCA.

With the exception of material 1.4591, all test plates exhibited a different, material-dependent weight loss. Furthermore, distinct discolorations of the surfaces were observed for all test plates. Both these weight losses and color changes depended directly on the exposure time of the test plates. They are greatest for materials 1.4404 and 1.4435, whereas materials 1.4539, 1.4591, 2.4600 and 2.4602 exhibited much smaller weight differences as shown in Figure 3.

It was possible to calculate material-specific corrosion rates from the weight losses (Figure 4). A positive value corresponds here to a decrease of material thickness, while a negative value indicates an increase, as is possible, for example, due to formation of an oxide/hydroxide layer.

On the basis of material analyses (ESCA), the discolorations of the test plates can be attributed to a layer formed in the course of the test from chromium(III) oxide ($Cr_2O_3$) or chromium(III) hydroxide ($Cr(OH)_3$ or respectively from nickel(III) oxide ($Ni_2O_3$) or nickel(III) hydroxide ($Ni_2O_3*H_2O$). (ESCA is unable to distinguish between oxides and hydroxides.) Compared with the matrix, material 1.4435 exhibited distinct changes down to depths of 200 to 250 nm, whereas for 1.4539 this is the case down to depths of only approximately 100 nm. For the investigated materials 1.4404, 1.4435 and 1.4539, the alloying element iron was almost completely absent in the near-surface layers (approximately 50 to 150 nm) (Figure 5).

The thickness of the oxide or hydroxide layer was determined from the half-height of the oxygen curve (red broken line in the ESCA profiles of the exposed test plates) and is presented in Table A. A possible explanation for the presence of magnesium down to sputter depths of 150 to 200 nm is the recycling of sodium hydroxide solution in this type of CIP plant. So magnesium contained in trace element solutions as used in biotechnological

**Figure 3** Weight variation of the test plates exposed to sodium hydroxide solution

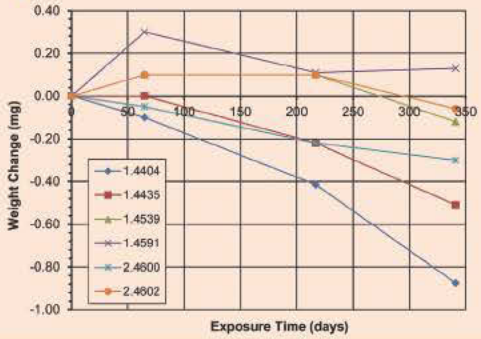
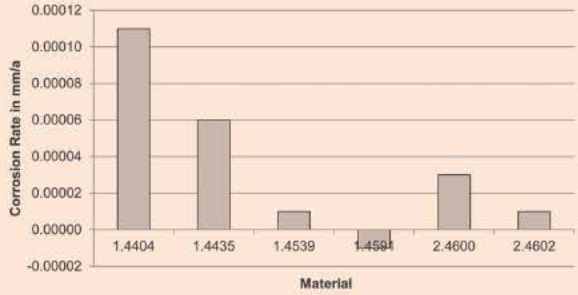



**Figure 4** Material-specific corrosion rates for the maximum exposure time of 354 days




fermentation processes could get into the sodium hydroxide CIP solution during cleaning of process equipment and finally enriched in the oxide/hydroxide layers of the exposed samples.

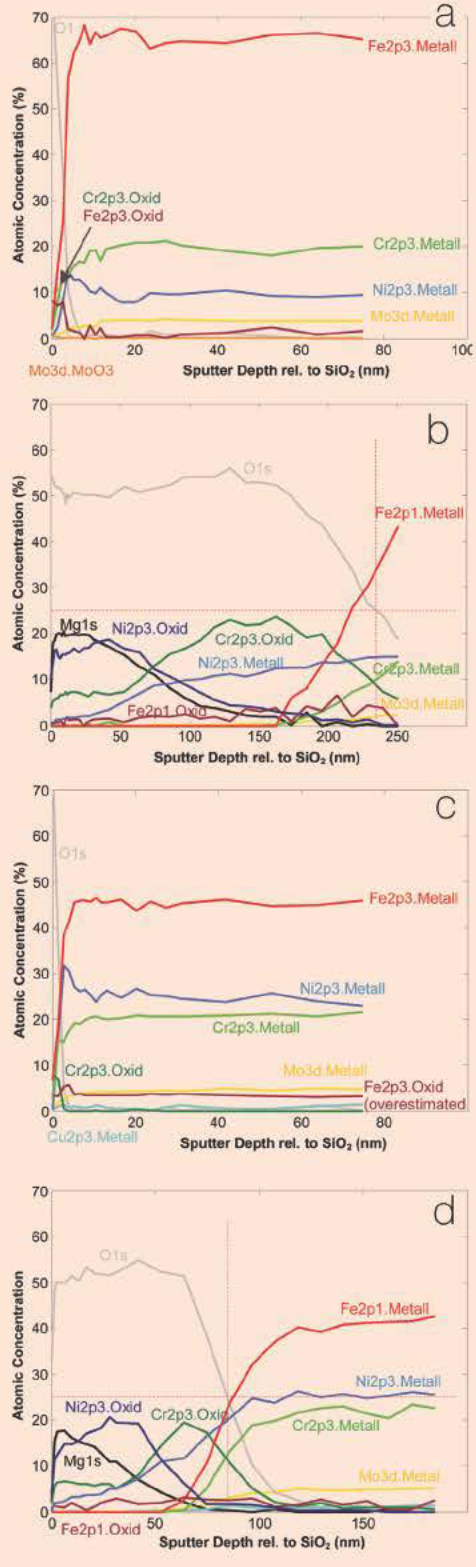
The SEM photographs revealed porous crystalline surface structures for material 1.4435, while material 1.4539 exhibits this to a much smaller extent (Figure 6).

The oxide layers formed during exposure to alkaline solution were bonded very stably with the surface and could not be removed by wiping. Thus release of particles into neighboring medium is not expected from such altered surfaces during the investigated exposure period. Nevertheless, the leaching of iron from the surface layers of the materials favors rouge formation in other system components. It may well be that the presence of atmospheric oxygen leads to oxidation of the iron hydroxide dissolved in the alkaline solution to sparingly soluble iron oxides, which are able to settle as migration rouge on system components.

**Table A** Half height of the oxygen curve of the material samples for the maximum exposure time of 354 days

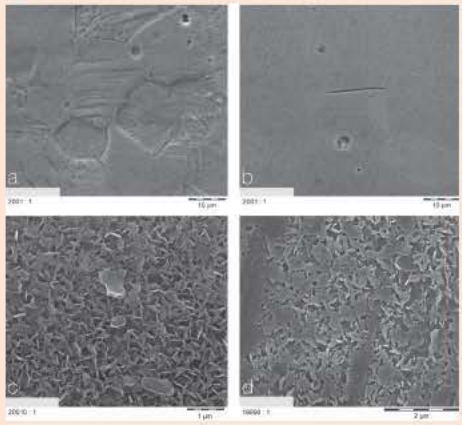
| Material | Relative Sputter Depth (nm) | |
|---|---|---|
| | Exposed | Reference |
| 1.4404 | 240 | ≤ 5 |
| 1.4435 | 40 | ≤ 5 |
| 1.4539 | 85 | ≤ 5 |

**Figure 5** ESCA depth profile




(a) reference material sample 1.4435, (b) material sample 1.4435 after exposure to NaOH, (c) reference material sample 1.4539 and (d) material sample 1.4539 after exposure to NaOH

Figure 6



(a) reference material sample 1.4435 [SEM photograph with a magnification of 2001:1; topography contrast (SE), 5 kV], (b) reference material sample 1.4539 [SEM photograph with a magnification of 2001:1; topography contrast (SE), 5 kV], (c) material sample 1.4435 after exposure to NaOH [SEM photograph with a magnification of 20,010:1; topography contrast (SE), 5 kV] and (d) material sample 1.4539 after exposure to NaOH [SEM photograph with a magnification of 19,890:1; topography contrast (SE), 5 kV]

Figure 7 Test plates of 1.4435

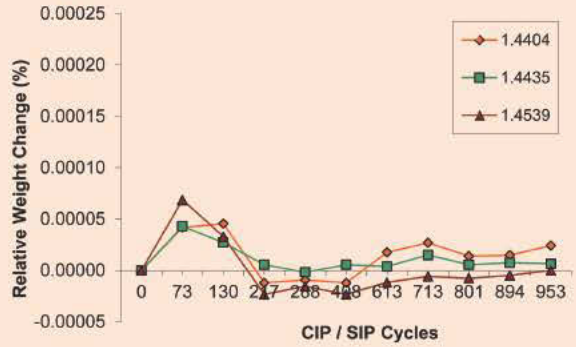

(a) front side and (b) back side – arrangement analogous to (a).
Note: 210, 211, 212 is upper zone of tank; 207, 208, 209 is lower zone of tank. 208 and 210 were subjected to derouging

## Rouge Formation due to Alternating Stress on Materials by Cleaning and Sanitizing Processes

To investigate the influence of the combination of cleaning and sanitizing processes on rouge formation, material-specific corrosion rates of various materials caused by exposure to various cleaning and sanitizing media were to be measured.

Electropolished test plates of materials 1.4404, 1.4435 and 1.4539 were subjected to combined cleaning/sanitizing cycles (10 minutes of rinsing with 1% sodium hydroxide solution; temperature ≥ 78°C; 30 minutes of sanitizing with clean steam: temperature > 121°C, 2.5 bar gauge). During cleaning with sodium hydroxide solution, one part of the test plates was above the liquid level, while the other part was immersed in the solution.

Figure 8 Weight variation of the test plates exposed to CIP/SIP




At the end of the test, all test plates exhibited reddish-brown discolorations typical of rouging on the surface, darker in the test plates that had been immersed in sodium hydroxide solution. Test plates 208 and 210, which had a distinctly paler appearance, were subjected after half of the test period to acid-based derouging, in order to check the resistance of these materials to an acid derouging chemical (Figure 7). After completion of derouging, these test plates were further exposed to the cleaning/sanitizing cycles.

A significant change in weight of the test plates due to rouge formation could not be observed. Because of the very small and non-uniform weight changes, it was not possible to determine material-specific corrosion rates. At this juncture, therefore, a graph of the relative weight change versus experiment time was chosen (Figure 8). The supposed weight increase at the beginning of the test (73 and 130 CIP/SIP cycles respectively) was attributed to inadequate rinsing of the test plates, such that residues of the sodium hydroxide solution were not completely removed.

It is highly likely that the slight weight increase in the further course of the test (from cycle 217 on) can be explained by the adsorption of oxygen in the oxide-rich rouge layer being built up in conjunction with the lack of material removal from this layer.

Table B Components and the respective investigations carried out on them

| Object | Optical Finding | SEM Investigation | ESCA Analysis | AES Analysis |
|---|---|---|---|---|
| Spray ball in a PW storage tank | x | | x | x |
| Filter of a WFI system | x | x | x | |
| Wipe sample from the surface of a WFI system | x | x | | |

Figure 9 Spray ball in a PW storage tank

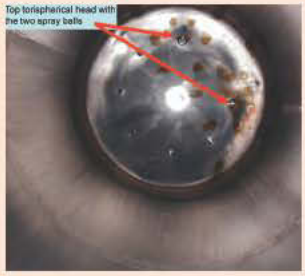



Figure 10 Dismantled spray ball from a PW storage tank

Figure 11 Depth profile by ESCA of the reddish inner surface of the spray ball

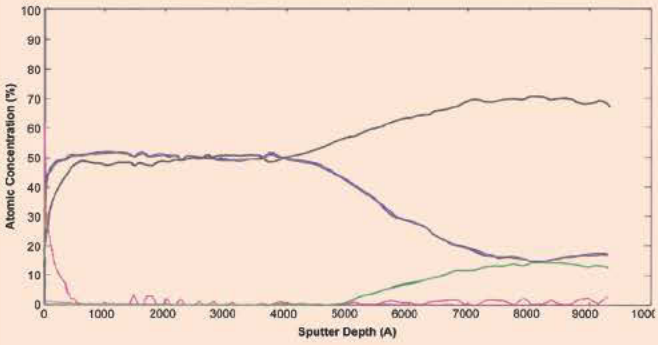



Figure 12 Filter of WFI system with discolored bluish inside surface

**Investigations by Surface Analysis and Determination of the Corrosion Rate of Components from Purified Water Systems**

Investigations were carried out on rouged components from various WFI systems in order to obtain more information about the actual buildup of rouge layers, which are formed in such systems. The investigations carried out on the respective components are presented in Table B and respective stress conditions listed in Table C. The detailed results for the individual components are presented below.

*Spray Ball of a PW Storage Tank*

The tank exhibits local surface discolorations, in particular precisely where the sprayed water impacts the tank surface (Figure 9). The spray ball itself exhibits yellowish to slightly reddish discolorations only on the supply tube (Figure 10). The inside surface exhibits an intense reddish coating. This was further investigated by surface-analysis techniques. In particular, depth profiles were surveyed by means of Auger electron spectroscopy (AES) and ESCA, in order to determine the variation of the alloying elements over the depth (Figure 11).

The samples were degreased and sputtered before the spectroscopic investigations, in order to remove potential carbon-containing impurities that may have been introduced by handling after dismantling. In both cases, it was found that the layer is approximately 600 nm thick and consists predominantly of iron and oxygen. This iron is present as FeO and FeO(OH). The other alloying elements – chromium, nickel and molybdenum – were not found.

*Filter from a WFI System*

A comparable result was found on a filter from a WFI system. The filter had been in service for approximately 6 months at 80°C, in a flow arriving from the inside. The outside surface has a slightly brownish appearance, while the discoloration of the inside surface is predominantly bluish (Figure 12). Only the attachment zone and the tip are metallically bright. The SEM investigation undertaken revealed that the bluish surface is formed from a closed layer consisting of many fine crystals. The average crystal size is approximately 0.2 µm. In contrast, only individual particles with a size of 0.1 µm can be observed in the metallically blank zone (Figure 13).

The depth profile recorded by means of ESCA (Figure 14) shows the variation of the alloying elements down to a depth of approximately 100 nm. The high carbon and silicon contents directly at the surface can be attributed to the adsorption of $CO_2$ and silicone compounds, which among other possibilities presumably reached the surface during handling after service. Because the surface is highly structured, these impurities can be measured to even greater depths. The layer is more than 120 nm thick, since oxygen contents of > 25% were still determined down to this zone and significant contents of carbon and silicon are also still present. In the first 60 nm, the chromium content is very low, while nickel and molybdenum are virtually absent.

Iron and chromium are present directly at the surface as $Fe^{3+}$ and $Cr^{3+}$ respectively.

*Condition of a WFI System*

A WFI system was optically appraised by opening the system at several places and investigating the coatings there by means of SEM and EDX. The results for the rouged zones are summarized in Table F.

The coatings were picked up from the surface by means of a cloth and then analyzed by means of SEM. The coatings contained predominantly oxygen, iron and chromium. Samples that were presumably rubbed more vigorously also exhibited nickel and a relatively low oxygen content (Figure 15).

*Summary*
The surface of metallic materials such as 316L is altered during rouge formation. The passive layer, which is a few nm thick and has a high chromium content, is changed to an iron-rich layer that also has relatively low contents of chromium and nickel. Depending on time and nature of the exposure, the layer thickness grows to more than 600 nm. The surface texture is changed from metallically smooth to a crystalline structure.

In order to simulate the rouging process and to investigate it further as regards the buildup of the rouge layer and the corrosion rate, electropolished seamless base-metal samples of various austenitic standard materials were aged in a WFI distillation system showing signs of rouging. The exposure time was 21 days at 108°C. The results of the optical examination and of the gravimetric evaluation are summarized in Table G.

When the samples were removed, they exhibited a metallically bright surface and no signs of rouging. The measured rates of material removal ranged from $4*10^{-4}$ to $18*10^{-4}$ mm/a.

**Heavy Metal Concentrations in Purified Water Systems and Active Substance Solutions**
During monitoring of PW/WFI systems, it is common practice to determine, among other parameters, the heavy metal ion concentration in the water. According to the European Pharmacopoeia 6.2 (2008), a total limit value of < 100 ppm is defined for this. The limit values according to the EMEA Guideline for active substance solutions are differentiated according to the individual metal species and are much lower for the elements other than iron and zinc. They are therefore used as reference. The results of water analysis from various circuits are summarized in Table H. ICP MS was used for the determination.

The results show that, in a normally operated water circuit in which fresh water is regularly injected and removed, no measurable enrichment of heavy metal ions takes place and their concentrations are below the limit values of the EMEA Guideline by a factor of 10.

Under non-typical operating conditions, in which the water is merely circulated in the circuit for weeks, for example to prevent a hygiene risk to the system during a production shutdown, an increase of the nickel content due to enrichment may occur. In such exceptions, it should be checked, for example by analyses, whether a limit value violation exists and whether the water purity may have to be adjusted safely below the limit values by partial or complete replacement of the water.

Furthermore, it was investigated whether active substance solutions produced in production systems made of structural

| Table C | Stress conditions of the investigated components | | | | |
|---|---|---|---|---|---|
| Water Quality | Temperature | Hot Steps | Material | Appearance | Age |
| PW | 40°C | 85°C once per year (5 h) | 1.4571<br>1.4404 | ▸ Tank localized points<br>▸ Spray ball inside complete reddish | n/a |
| WFI | 80 | None | 1.4571<br>1.4404 | Outside: brownish<br>Inside: bluish | 6 months |
| WFI | > 80°C | None | 1.4571<br>1.4404 | See Table I | 24 years |

materials 1.4435 exhibit elevated heavy metal concentrations. For this purpose, the heavy metal concentration of active substance solutions from various systems of different age was investigated.

Table I shows the systems in question with the year when they were placed in service and the respective active substance solution produced in the system. At the end of the production process, samples of three successive batches of the respective active substance were investigated by means of ICP MS to determine their heavy metal concentration.

For all investigated API samples, the results of the heavy-metal analysis were below the limit of quantitation of the analysis method and therefore well below the requirements of the EMEA[12], regardless of the degree of rouging and of any derouging actions that may have been performed.

**Influence of Rouge Coatings on Cleaning Efficiency**

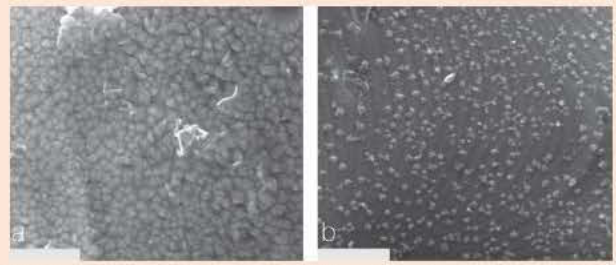
The cleanability of rouged material surfaces was investigated.

Rouging was caused in a test tank by a rapid sequence of combined cleaning/sanitizing cycles (10 minutes of cleaning with 1% sodium hydroxide solution, temperature ≥ 78°C, then 30 minutes of sanitizing with clean steam at > 121°C, 2.5 bar gauge), and the material surface was exposed to protein solution at periodic intervals. After the protein solution had dried, the test tank was cleaned and then analyzed for protein residues.

The test system was constructed such that it corresponded to the customary conditions in pharmaceutical production with respect to material (material grade), cleaning/sanitizing method used (time, temperature, cleaning medium, concentration of the cleaning medium) and model contamination (aqueous solution of a monoclonal antibody). Differences compared with the surfaces used in production consisted in the mechanically instead of electropolished surface of the test tank. In this connection, it must be pointed out that mechanically polished surfaces are more difficult to clean because of their larger true surface, in addition to which they accelerate rouge formation.

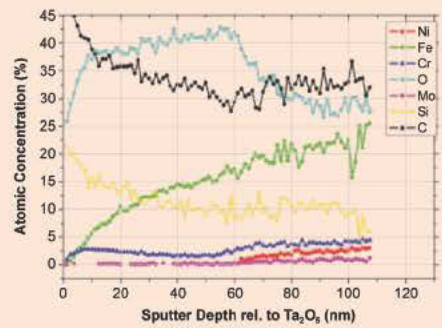
| Table D | AES analysis of spray ball (element concentration in atom percent) | | | | | | |
|---|---|---|---|---|---|---|---|
| Location | C | O | S | Ca | Cr | Fe | Ni |
| Surface | 66 | 21 | 1 | 4 | - | 9 | - |
| Mid Profile | - | 47 | - | - | - | 53 | - |
| Post Profile | 6 | 18 | - | - | 11 | 57 | 8 |

Figure 13 SEM analysis



(a) bluish discolored inside surface and (b) metallic bright inside surface

Figure 14 ESCA depth profile of bluish inside surface

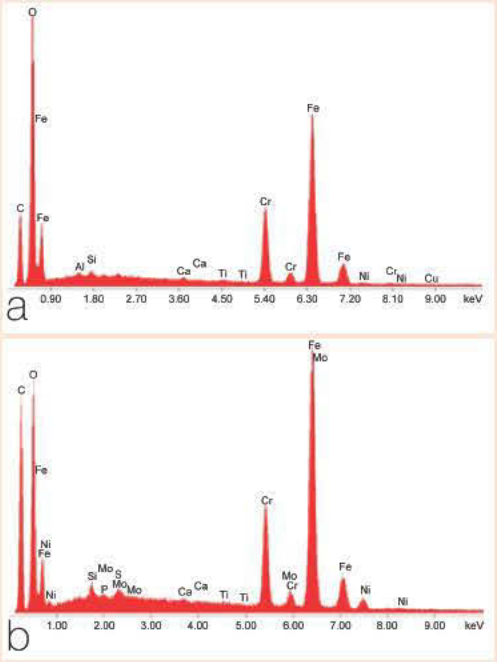



With increasing number of cleaning/sanitizing cycles, the rouging increased distinctly and the inside surface of the test tank exhibited an increasingly intensive reddish-brown color over the test duration. Four zones with rouging of different intensity and stability were formed (Figure 16).

- Zone 0: no externally applied heating jacket
- Zone 1: externally applied heating jacket
- Zone 2: externally applied heating jacket, below the liquid level, without migration rouge
- Zone 3: externally applied heating jacket, below the liquid level, with migration rouge

The formation of these different zones was explained by different heat influences of the heating jacket and by the times of exposure to the various media (sodium hydroxide solution, clean steam).

**Figure 15** EDX analysis




(a) tank surface sample and (b) diaphragm valve at upper tank section

**Figure 16** Classification of the interior space of the test tank into zones with different rouge formation

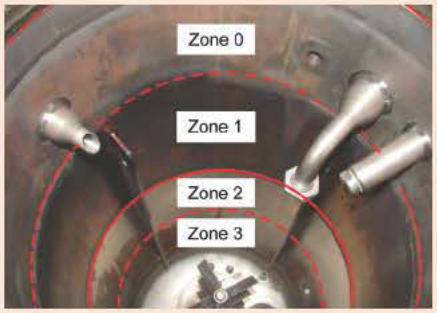



**Figure 17** Results of the TOC and Swab analyses

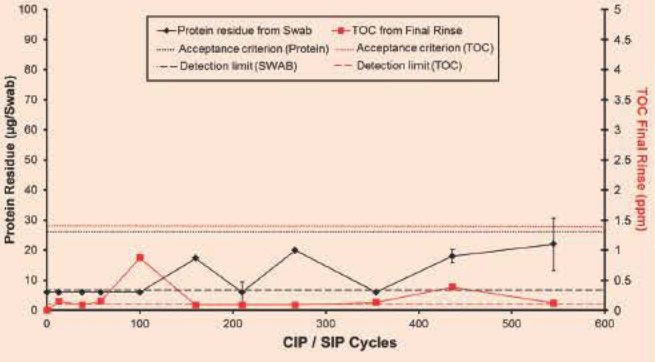
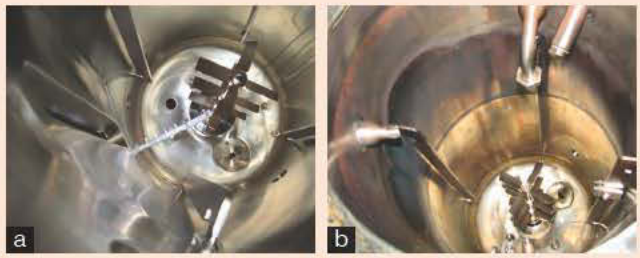



**Figure 18** Test tank




Before the beginning of the test (L) and after 545 cleaning/sanitizing cycles (R)

To measure potentially present protein residues, residue determinations were carried out using polyester fabric cloths (swabs) and TOC analyses of the post-rinse water of the cleaning process.

Even though the rouge formation increased strongly over the test period, these analyses did not reveal any trend. In all cases, the results of both analyses methods were below the specified limit values. The limit values used were derived from PI 006-3.28 Despite the very intensive rouging, no significant impairment of the cleaning efficiency was observed (Figure 17). The visual surface conditions of the test tank are illustrated in Figure 18.

Tests and practical experiences addressing further risks and influencing factors according to Table G in Part 1 will be described in Part 3 of this article.

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**Table E** ESCA analysis of spray ball (element concentration in atom percent)

| Location | Na | Zn | Fe | O | N | Ca | C | Cl | S | Si | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Degrease and Sputtered Surface | 0.5 | - | 30.1 | 46.3 | 3.3 | 0.6 | 17.2 | 0.2 | 0.2 | 1.6 | - |

**Table F** Results of optical inspection and SEM analysis of wipe samples

| Components | Optical Appearance | SEM Analysis of Wipe Samples |
|---|---|---|
| Buffer tank | Reddish discoloration, particularly above the lower weld seam Upper tray showing slight multi-colour discoloration | Especially oxygen, iron and chromium were determined in the coatings. Trace amounts of nickel and molybdenum were also present |
| Lower connection piece | Slight reddish discoloration | Small oxygen content; composition of the alloying elements iron, chromium nickel and molybdenum conform to the alloy content of the material of construction |
| Diaphragm valve at upper tank section | Slight reddish discoloration | A greater oxygen content again shows a defined iron and chromium peak and diminishing nickel and molybdenum contents |

**Table G** Corrosion rate of standard austenitic stainless steels, 108°C, 21 days

| Material No. | Number of Samples | Corrosion Rate (mm/a) | Appearance |
|---|---|---|---|
| 1.4301 | 1 | 0.0018 | Metallic bright |
| 1.4571 | 1 | 0.0004 | Metallic bright |
| 1.4404 | 4 | 0.0004 - 0.0014 | Metallic bright |
| 1.4435 | 1 | 0.0010 | Metallic bright |

**Table H** Heavy metal concentrations in various water circuits, determination by means of ICP MS

| Unit | Fe (ppm) | Cr (ppm) | Ni (ppm) | Mo (ppm) |
|---|---|---|---|---|
| Unit 1: Deionized water | 1.8 | < 0.1 | < 0.1 | < 0.1 |
| Unit 1: WFI hot normal operation | < 1.0 | 0.13 | 0.16 | < 0.1 |
| Unit 1: WFI cold | < 1.0 | < 0.1 | 0.18 | < 0.1 |
| Unit 1: WFI after 12 days without water withdrawal | < 1.0 | < 0.1 | < 1.0 | < 0.1 |
| Unit 2: WFI normal operation | < 1.0 | < 0.1 | < 1.0 | < 0.1 |
| Unit 2: WFI after two month without water withdrawal | < 1.0 | < 0.1 | 6.6 | < 0.1 |
| Limit of Quantitation (ICP-MS) | 1.0 | 0.1 | 0.1 | 0.1 |
| Limit value (EMEA Guideline) | 130 | 2.5 | 2.5 | 2.5 |

**Table I** Heavy metal concentrations of various active pharmaceutical ingredients from different production systems.

| Production System | API (Active Substance) | Plant placed in service (year) | Derouging (year) | Fe (ppm) | Mn (ppm) | Ni (ppm) | Cr (ppm) | Mo (ppm) |
|---|---|---|---|---|---|---|---|---|
| System 1 | API 1 | 1998 | 2008 | < 0.6 | < 0.06 | < 0.09 | < 0.06 | < 0.02 |
| System 2 | API 1 | 2006 | n/a | < 0.6 | < 0.06 | < 0.09 | < 0.06 | < 0.02 |
| System 2 | API 2 | 2006 | n/a | < 0.6 | < 0.06 | < 0.09 | < 0.06 | < 0.02 |
| System 3 | API 3 | 2003 | n/a | < 0.6 | < 0.06 | < 0.09 | < 0.06 | < 0.02 |
| System 4 | API 3 | 2005 | n/a | < 0.6 | < 0.06 | < 0.09 | < 0.06 | < 0.02 |
| System 5 | API 4 | 2004 | 2008 | < 0.6 | < 0.06 | < 0.09 | < 0.06 | < 0.02 |
| System 5 | API 5 | 2002 | 2008 | < 0.6 | < 0.06 | < 0.09 | < 0.06 | < 0.02 |
| Limit of Quantitation (ICP-MS) | | | | 0.6 | 0.06 | 0.09 | 0.06 | 0.02 |
| Limit (EMEA Guideline) | | | | 130 | 25 | 2.5 | 2.5 | 2.5 |

*Date of the retention samples of the investigated products: May to December 2010; analyses were performed from November 2010 to March 2011*

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## AFRICA

### Ghana

*Ghana FDA Expresses Concern over Porous Borders*[1]

GhanaWeb reports that the Ghanaian Food and Drugs Authority (FDA) expressed concern over the porous nature of the country's borders. According to the Chief Executive Officer of the FDA, Mr. Hudu Mogtari, medicines approved for importation mandatorily go through the Tema Port and the Kotoka International Airport. However, many unapproved routes dotted along the borders of the country serve as entry points for drugs that escape the scrutiny of the authority's officials. Preventing unauthorized drugs from entering the market costs the agency heavily in human resources, fuel for vehicles, security and sometimes money to buy products suspected to be fake for testing.

### Ethiopia

*PQAD Attained International Laboratory Accreditation*[2]

To better ensure the quality of medicines in Ethiopia, the country's medicines quality control laboratory – the Product Quality Assessment Directorate (PQAD) – has attained the internationally recognized ISO/IEC 17025:2005 accreditation for testing and calibration laboratories. PQAD serves as the technical wing of the Ethiopian Food, Medicine and Health Care Administration and Control Authority, protecting the quality of food and medicines both before market authorization and while they are on the Ethiopian market.

## AUSTRALIA

*TGA Key Performance Indicators: July to December 2014*[3]

The Australian Therapeutic Goods Administration (TGA) regularly publishes information on key performance indicators (KPI), which are aligned with its strategic plan. These indicators are: 1) Stakeholder communication, education and satisfaction; 2) Premarket business operations; 3) Postmarket business operations; 4) Organizational health; 5) Financial performance 6) Statutory obligations; 7) International cooperation; and 8) Decision making. TGA recently published a KPI report covering aspects of performance between July and December 2014. Progress has been made in a number of areas since the last KPI report. In particular, there has been continued improvement in performance in stakeholder communication, education and satisfaction. There were also several significant outcomes in efforts towards greater international harmonization, information sharing and cooperation. The report can be found at https://www.tga.gov.au/publication/tga-key-performance-indicators-july-december-2014.

*Searching the TGA Website*[4]

The TGA published a video overview of how to search the TGA website - focusing on the Australian Register of Therapeutic Goods and other specialized databases, and where to search for specific information. This video can be found at https://www.tga.gov.au/searching-tga-website.

## ASIA

### China

*China to Implement Drug Distribution Reform*[5]

Reuters reports that China has announced plans to implement drug distribution reforms including centralization measures designed to cut prices and reduce corruption. Drug manufacturers are being urged to negotiate directly with hospitals on payment for pharmaceuticals instead of going through middle men. Additionally, authorities will push forward centralization and standardization measures in an effort to weed out corruption and lower prices. Work will also be done to ensure the distribution of drugs to remote rural areas with underdeveloped modes of transportation in a timely fashion.

*CFDA and US FDA China Office Hold the First Working Meeting of 2015*[6]

On 11 February 2015, the Department of International Cooperation of China Food and Drug Administration (CFDA) and the US Food and Drug Administration (FDA) China Office held the first working meeting of 2015. Officials reviewed and summarized the bilateral cooperation in exchange of high-level visits, GMP inspection and personnel exchanges in 2014, and studied and discussed the tasks of 2015.

*CFDA Issues Guiding Opinions on Enhancing the Construction of Food and Drug Inspection and Testing System*[7]

To further enhance the construction of the food and drug inspection and testing system and better play the role of inspection and testing as technical support, China Food and Drug Administration (CFDA) formulated the Guiding Opinions on Enhancing the Construction of Food and Drug Inspection and Testing System. The Guiding Opinions was adopted at the minister's working meeting of CFDA on 18 December 2014 and was issued on 23 January 2015.

*CFDA Issues "Good Supply Practice for Medical Devices"* [8]

To strengthen the quality management of medical device distribution, standardize medical device distribution behaviors, and guarantee the safety and effectiveness of medical devices, China Food and Drug Administration (CFDA) formulated the "Good Supply Practice for Medical Devices" in accordance with the newly revised "Regulations for the Supervision and Administration of Medical Devices" and the "Administrative Measures for the Supervision of Distribution of Medical Devices." "Good Supply Practice for Medical Devices" is comprised of 66 articles in nine chapters, which requires medical device distribution enterprises to set up and improve the quality management system in accordance with this document, and apply effective quality control measures in the purchase, acceptance, storage, sales, transportation, and after-sales service of medical devices to guarantee their quality and safety in the distribution process.

*CFDA Issues Technical Guideline for Development and Evaluation of Biosimilars*[9]

In order to guide and standardize the development and evaluation of biosimilars and promote the sound development of biomedicine industry, China Food and Drug Administration (CFDA) issued the "Technical Guideline for Development and Evaluation of Biosimilars (interim)," and specified relevant requirements on the application procedure, registration classification, and application documents of biosimilars.

### India

*CDSCO and US FDA Plan Close Working Relationship as US Expands Its Activities in India*[10]

A team of delegates from the US FDA recently met with CDSCO to enhance collaboration as exports from India to the US increase. They discussed the importance of firms enhancing their own "quality cultures." The US FDA will be piloting a new questionnaire that could be used to further standardize inspections, with the goal of uniformly harvesting the kind of data that supports accurate measures of quality. By improving the inspection process in this way, future "metrics" that define quality will be understood and aspired to by manufacturers – no matter where they are in the world.

## EUROPE

### European Union

*EU Task Force to Implement New International Standards on Identification of Medicines*[11]

The European Medicines Agency (EMA) is establishing a task force for the implementation of international standards for the identification of medicinal products for human use in the European Union (EU). The Agency is inviting interested parties to express their interest in being part of the task force. These standards are expected to simplify the exchange of information between regulatory authorities across the world and to support healthcare authorities in the development of electronic health records. They should also improve the safety monitoring of medicines by facilitating the assessment of data across classes of medicines and therapeutic areas.

*Twentieth Anniversary of EMA*[12]

26 January 2015 marked the 20th anniversary of the establishment of the European Medicines Agency (EMA). Founded in 1995, the Agency has worked across the European Union and globally to protect public health by assessing medicines to rigorous scientific standards and by providing partners and stakeholders with independent, science-based information on medicines. 2015 also marks the 50th anniversary of the introduction of the first EU legislation on human medicines. "Council Directive 65/65/EEC" of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products was adopted.

*Transitioning to Mandatory Use of Electronic Application Forms*[13]

The European Medicines Agency is announcing the transition to the mandatory use of electronic application forms for initial marketing authorizations, variations and renewals for human and veterinary medicines. As of 1 July 2015 it will be mandatory for companies submitting applications for centralized procedures to use the electronic application form. From 1 January 2016 the application forms in Word format published by the European Commission will no longer be available and only the latest version of the electronic application form will be used for all EU procedures, including national procedures.

*EU Publishes Guidelines on APIs and Excipients*[14]

The European Commission published two guidelines in the official journal of the European Union, edition 21st March 2015:

- *Guidelines on the Principles of Good Distribution Practice for Active Substances of Medicinal Products for Human Use*

  These guidelines provide stand-alone guidance on Good Distribution Practice for importers and distributors of active substances for medicinal products for human use. They complement the rules on distribution set out in the guidelines of EudraLex Volume 4, Part II, and apply also to distributors of active substances manufactured by themselves

- *Formalized Risk Assessment for Ascertaining the Appropriate Good Manufacturing Practice for Excipients of Medicinal Products for Human Use*

  The manufacturing authorization holder is required to ensure that the excipients are suitable for use in medicinal products by ascertaining what the appropriate good manufacturing practice (GMP) is. The appropriate GMP for excipients of medicinal products for human use shall be ascertained on the basis of a formalized risk assessment in accordance with this guideline. The risk assessment shall take into account requirements under other appropriate quality systems as well as the source and intended use of the excipients and previous instances of quality defects. The manufacturing authorization holder shall ensure that the appropriate GMP ascertained is applied. The manufacturing authorization holder shall document the measures taken.

### Denmark

*New Management at the DHMA*[15]

As from 13 March 2015, Jakob Cold has been appointed Acting Director General of the Danish Health and Medicines Authority (DHMA). Jakob Cold has been a member of the Board of Directors of the DHMA since October 2013 and is responsible for finance, IT, and radiation protection. Anne-Marie Vangsted will continue as Director with special responsibility for the DHMA's supervision. The organizational change is a consequence of the fact that Else Smith was removed from the position as Director General on 12 March 2015. The Ministry of Health will advertise the position as Director General for the DHMA.

### Hungary

*Hungarian Competent Authority For Human Medicines Reorganized*[16]

Due to extensive re-organization of governmental institutions in Hungary as ordered by the 28/2015 (II. 25.) Decree of the Government, from 1 March 2015 the name, address and bank account number of the competent authority for human medicinal products will change as follows:

Name: National Institute of Pharmacy and Nutrition
Address: 1051 Budapest, Zrínyi utca 3
Bank account number: 10032000-00290050-00000000 at the Magyar Államkincstár Budapesti és Pest Megyei Igazgatóság Állampénztári Iroda (Hungarian State Treasury)
Address: 1139 Budapest, Hungary, Váci street 71
IBAN number: HU55 10032000 00290050 00000000
SWIFT code/BIC code: MA NE HU HB

From 1 March 2015 all fees are required to be paid to the new bank account. Payments to the old bank account will be regarded as invalid.

**Iceland**

*New Executive Director of IMA*[17]

Rúna Hauksdóttir is the new Executive Directorof Icelandic Medicines Agency (IMA) as from 1 February 2015. She has an MS in Health Economics from the University of Iceland, MSC in BioPharmacy from King´s College, University of London and a Pharmacy degree from the University of Iceland. Previously she was the Chairman of the Icelandic Medicine Pricing and Reimbursement Committee and also a lecturer in pharmacoeconomics at the University of Iceland. Prior to that, she worked within the pharmaceutical industry.

*The IMA Introduces Electronic Signatures*[18]

As a part of the information and environmental policies, the Icelandic Medicines Agency (IMA) has recently prepared for the introduction of electronic signatures for regulatory documents and documented responses. When IMA issues an electronically signed document, signatures are supported by a qualified certificate issued by Auðkenni hf. validated by intermediate certificate "Íslandsrót" issued by the Ministry of Finance and Economic Affairs. An electronic signature with such qualified electronic certificates has the same legal effect as a handwritten signature.

**Switzerland**

*Agreement between Switzerland and China to Increase the Institutional Collaboration in the Areas of Foodstuffs, Medicinal Products, Medical Devices and Cosmetics*[19]

Switzerland and China attained a bilateral agreement intending to institutionalize a dialogue between the competent government authorities in areas of foodstuffs, medicinal products, medical devices and cosmetics. It will also deepen the exchange in these mutually beneficial areas relevant to health. Regular exchanges are intended to increase each other's understanding for the respective regulatory systems and legal frameworks in the two countries as well as build mutual trust.

**United Kingdom**

*MHRA Updates Good Manufacturing Practice and Good Distribution Practice*[20]

The updated GMP compliance report templates and guidance have been added to the GMP Page, which can be found at https://www.gov.uk/good-manufacturing-practice-and-good-distribution-practice.

## NORTH AMERICA

### Canada

*Health Canada Issues "Guidance Document on the Application for a Certificate of a Pharmaceutical Product"*[21]

Certificate of a Pharmaceutical Product (CPP) describes the procedure for the request of a CPP. A CPP, in the format recommended by the WHO, establishes the status of the pharmaceutical product listed on the certificate, and the GMP status of the fabricator of the pharmaceutical product, in the exporting country. This document supersedes the document of the same name issued 1 April 2014.

*Health Canada to Increase GMP Inspections, Transparency*[22]

In a letter dated 17 February, Health Canada informed all Drug Establishment License holders that it intends to increase the frequency of both planned and unplanned GMP Inspections. Beginning 1 April 2015, GMP inspections will be summarized and posted as part of Health Canada's Openness and Transparency Framework.

## UNITED STATES

*US FDA Commissioner Margaret Hamburg Steps Down*[23]

Dr. Margaret Hamburg, who was commissioner of the US Food and Drug Administration for almost six years, and only the second woman to hold this position, is stepping down. Dr. Stephen Ostroff, the FDA's chief scientist, will fill Hamburg's position until a new commissioner is named.

*FDA Issues Revised Draft Guidance for Industry on Disclosing Risk Information in Consumer-Directed Print Advertisements and Promotional Labeling for Human Prescription Drugs*[24]

This revised draft guidance provides recommendations on the disclosure of risk information in prescription drug product advertisements and promotional labeling in print media directed toward consumers with respect to the brief summary requirement and the requirement that adequate directions for use be included with promotional labeling. The recommendations describe an alternative disclosure approach that FDA refers to as a consumer brief summary. This revised draft guidance does not focus on the presentation of risk information in the main body of promotional labeling or advertisements and does not apply to promotional materials directed toward health care professionals.

*FDA Addresses Regulation of Medical Apps and Accessories*[25]

The FDA finalized guidance on medical device data systems, and issued two draft guidance documents that outline the thinking about low-risk devices intended to promote general wellness, and the risk classification approach to medical device accessories. The FDA committed to issue these guidances in the *FDASIA Health IT Report* of April 2014.

*FDA Launches Drug Shortages Mobile App*[26]

The US Food and Drug Administration launched the agency's first mobile application (app) specifically designed to speed public access to valuable information about drug shortages. The app identifies current drug shortages, resolved shortages and discontinuations of drug products. Drugs in short supply can delay or deny needed care for patients. Drug shortages may also lead health care professionals to rely on alternative drug products, which may be less effective or associated with higher risks than the drug in shortage.

*How Does the Pharmaceutical Industry Really Work? FDA Wants its Managers to Know*[27]

"The Center for Drug Evaluation and Research (CDER) has announced that it plans to continue a program which allows pharmaceutical companies to invite regulators to visit their manufacturing sites to better understand how the industry operates," recently reported Regulatory Affairs Professional Society News.

"The goals of the 'Site Tours' program are to provide firsthand exposure to the industry's drug development process, a venue for sharing information about regulatory project management (but not drug-specific information) and an opportunity for CDER's regulatory project managers to fulfill an industry site tour requirement... The site tours also feature 'daily workshops' [with the] primary objective to learn about the team approach to drug development, including drug discovery, preclinical evaluation, tracking mechanisms and regulatory submission operations."

*Regulatory Site Visit Training Program*[28]

The Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) announced an invitation for participation in its Regulatory Site Visit Training Program (RSVP). This training program is intended to give CBER regulatory review, compliance, and other relevant staff an opportunity to visit biologics facilities. These visits are intended to allow CBER staff to directly observe routine manufacturing practices and to give CBER staff a better understanding of the biologics industry, including its challenges and operations. The Federal Register notice inviting biologics facilities to contact CBER for more information if they are interested in participating in this program.

*FDA Publishes Guidance Document: "Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities Guidance for Industry"*[29]

This guidance sets forth the Food and Drug Administration's policy regarding repackaging by state-licensed pharmacies, Federal facilities, and facilities that register with the FDA as outsourcing. It describes the conditions under which FDA does not intend to take action for violations when a state-licensed pharmacy, a Federal facility, or an outsourcing facility repackages human prescription drug products.

*New Guidance Document Search Feature*[30]

A new feature on the FDA.gov website allows you to search for guidance documents for all topics across the site from one convenient location: http://www.fda.gov/RegulatoryInformation/Guidances/default.htm




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## SOUTH AMERICA

### Argentina

*ANMAT Releases New Publication*[31]

The ANMAT, Argentina's drug regulatory agency, has published a new publication which reports on the activity carried out by the different areas of the Administration. The first issue contains articles on the National Traceability System for Drugs, the area of Health Technology Assessment, the participation of agency activities in the country and abroad, and a photo tour digital signature area. The publication appears every three months and will be sent to subscribers via email. It will also be available on their website.

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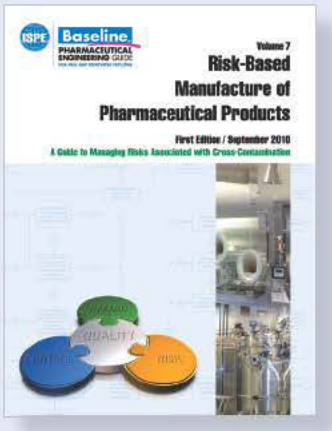
## NEW EUROPEAN EXPECTATIONS ON CROSS-CONTAMINATION

**Medicinal products, while providing (sometimes lifesaving) benefits for their recipients, can pose significant risks if they become cross-contaminated or if their active ingredients contaminate other products.** Cross-contamination becomes a concern when different medicinal products are produced in the same facility. Chapters 3 and 5 of the EudraLex Volume 4 have been updated "to provide improved guidance on the prevention of cross-contamination," and introduce a preinspection risk- based assessment.

These revised guidelines came into effect on the 1 March 2015. They have been amended to promote a science- and risk-based approach, and recommend a "toxicological evaluation"—Acceptable Daily Exposure (ADE) and Permitted Daily Exposure (PDE)—to establish threshold values for risk identification. The old 10-ppm rule of thumb is no longer accepted without justification. Dedicated facilities are required for substances for which no lowest threshold level is known, and for those for which cleaning can't be validated under the PDE-based limit. Certain product categories are still excluded, such as beta-lactam antibiotics. The EudraLex Annex 15 has also been updated, effective 1 October 2015, with references to the need for a toxicological evaluation in setting limits for product carryover during cleaning validation.

Both chapters and the Annex reference the European Medicines Agency's "Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities," which was adopted by the EMA in November 2014. This guideline recommends an approach for deriving a scientifically based threshold value for individual active substances to be applied for risk identification. It outlines how the data on which the threshold value is derived should be presented to achieve a clear and harmonious approach across the pharmaceutical industry.




*ISPE's Baseline Guide®: Risk-Based Manufacture of Pharmaceutical Products* (Risk-MaPP) provides a scientific risk-based approach, based on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidance for Industry Q9: "Quality Risk Management," to manage the risk of cross-contamination. The Risk-MaPP Guide is being updated to ensure consistency with the new EU guidelines, and is expected to be available later this year. Its goal continues to be to help companies achieve and maintain an appropriate balance between product quality and product safety. Originally published in 2010 in partnership with international industry experts and global regulators, the first edition introduced the ADE concept, which is similar to the approach the EMA has now adopted. The current edition of the Guide was already very much aligned with the recently published EU expectations, and will be updated to refer to the new EMA/EU documents, map the terminology for ADE and PDE, and reflect the ongoing deeper understanding of the ICH Q9 process.

Using a risk-based model to prevent cross-contamination helps to ensure the safety of patients, and it also makes good business sense. Such a model allows the presence of contaminants to be managed according to the risk posed. Manufacturers who know their products, processes and facilities best can make better decisions using this information. Additionally, resources can be allocated appropriately to reduce wasted time and effort on low risk areas. Good risk management can also positively impact a firm's relationship with regulators. As ICH Q9 notes: "Effective quality risk management can . . . provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight." And as regulators in all regions increasingly establish inspection frequency based on risk, precious industry and regulator resources can be focused on those areas that benefit our patients most. [1,2,3]

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**Medicine by Numbers**

*The Economist, Technology Quarterly, March 7, 2015*

"If we didn't take any risks, we wouldn't approve any drugs," says Susan Ellenberg, a professor of biostatistics at the University of Pennsylvania. "Some people will always want a new drug sooner and say they're willing to take a chance. Others will ask, why didn't you study it longer and find out about this horrible side-effect?"

During her long career, Dr Ellenberg has used data to quantify and communicate those risks. Along the way she has helped to shape a discipline that owes as much to ethics and philosophy as it does to pure mathematics. Now medicine is entering a new digital age, one of Big Data and high-tech personalised treatments that are tailored to an individual's genetic make-up.
http://www.economist.com/news/technology-quarterly/21645510-susan-ellenberg-biostatistician-trying-avoid-mistakes-era-big-data

**When the Hospital's Drug Cabinet is Bare**

*The Washington Post, April 24, Lenny Bernstein*

I worry about a lot of things that could go wrong if I'm taken to a hospital, but until today this hasn't been one of them: Hospitals are routinely running short of critical antibiotics, often for months at a time. When Larissa May, an associate professor of emergency medicine at George Washington University, and a team of researchers checked, they found that hospitals across the country ran short of 148 anti-bacterial drugs over a 13-year period, from 2001 to 2013.
http://www.washingtonpost.com/news/to-your-health/wp/2015/04/24/when-the-hospitals-drug-cabinet-is-bare/

**What Pushes Scientists to Lie? The Disturbing But Familiar Story of Haruko Obokata**

*The Guardian, February 18, John Rasko and Carl Power*

The year 2014 was one of extremes for Haruko Obokata. A year of high highs and even lower lows. Barely 30 years old, she was head of her own laboratory at the Riken Center for Developmental Biology (CDB) in Kobe, Japan, and was taking the male-dominated world of stem cell research by storm. She was hailed as a bright new star in the scientific firmament and a national hero. But her glory was short-lived and her fall from grace spectacular, completed in several humiliating stages.
http://www.theguardian.com/science/2015/feb/18/haruko-obokata-stap-cells-controversy-scientists-lie

**Speedy Drug Approvals Have Become the Rule, Not the Exception**

*New York Times, May 1, 2015, Margot Sanger-Katz*

Congress has over the past few decades passed a series of special approval pathways for important drugs that treat life-threatening or rare diseases. This week, a new bill introduced in the House could add two more.
http://www.nytimes.com/2015/05/02/upshot/speedy-drug-approvals-have-become-the-rule-not-the-exception.html

**FDA Ponders Putting Homeopathy To A Tougher Test**

*NPR Radio News, 20 April 2015, Rob Stein*

In 1988, the Food and Drug Administration decided not to require homeopathic remedies to go through the same drug-approval process as standard medical treatments. Now the FDA is revisiting that decision. It will hold two days of hearings this week to decide whether homeopathic remedies should have to be proven safe and effective.
http://www.npr.org/blogs/health/2015/04/20/398806514/fda-ponders-whether-homeopathy-is-medicine

**Most Countries Not Protecting Antibiotics, Says WHO**

*BBC, 29 April 2015, James Gallagher*

Three-quarters of countries do not have plans in place to preserve antimicrobial medicines, the World Health Organization says. The body has repeatedly warned that the globe is heading into a "post-antibiotic era" in which much of modern medicine becomes impossible.
http://www.bbc.com/news/health-32515967

**Should Companies Have to Pay for Disposal of Unwanted Drugs?**

*Wall Street Journal, 1 May 2015, Ed Silverman*

Should drug makers be required to pay for take-back programs in which consumers can drop off unwanted medicines? A growing number of local officials believe they should. Earlier this week, San Mateo County in California became the fourth local government in the country to adopt an ordinance that mandates the pharmaceutical industry underwrite the costs of a take-back program.
http://www.wsj.com/articles/should-companies-have-to-pay-for-disposal-of-unwanted-drugs-1430487007?tesla=y

**Time to Prove Hospital Disinfectants Work, FDA Says**

*NBC News, 30 April 2015, Maggie Fox*

Hospital workers wash their hands hundreds of times a day. Nurses are constantly using alcohol gels, chemical wipes and iodine washes on themselves and on patients. Now that there's a hand sanitizer dispenser at every hospital room door, it's time to check that they actually do work as well as everyone assumes and that they are safe, the Food and Drug Administration says.
http://www.nbcnews.com/health/health-news/time-prove-hospital-disinfectants-work-fda-says-n351421

**Antibiotic Shortages on the Rise in US**

WebMD *News from HealthDay, 23 April 2015, Steven Reinberg*

Shortages of antibiotics, including those used to treat drug-resistant infections, may be putting patients at risk for sickness and death, according to a new report. Between 2001 and 2013, there were shortages of 148 antibiotics. And the shortages started getting worse in 2007, researchers found.
http://www.webmd.com/news/20150423/antibiotic-shortages-on-the-rise-in-us

### AmpliPhi Biosciences Announces M. Scott Salka as New CEO

*AmpliPhi BioSciences Corporation, 30 April 2015*

AmpliPhi BioSciences Corporation, a global leader in developing bacteriophage-based antibacterial therapies to treat drug resistant infections, today announced that Scott Salka has been appointed as the new CEO. Mr. Salka will replace Interim CEO and Chairman of AmpliPhi, Jeremy Curnock Cook, effective May 18. Mr. Curnock Cook will remain in his role as Chairman.

### Simulations Plus Releases GastroPlus Version 9.0

*Simulations Plus, Inc., 30 April 2015*

Simulations Plus, Inc. (NASDAQ: SLP), a leading provider of simulation and modeling software for pharmaceutical discovery and development, today announced that it has released the long-awaited Version 9.0 of its flagship GastroPlus™ simulation software. Dr. Michael Bolger, chief scientist of Simulations Plus, said: "We're very pleased to announce the release of GastroPlus Version 9.0. This is the largest single upgrade we've made to the program to date, and the level of science and technology adds valuable new functionalities that we believe will provide the most advanced decision-making tool for preclinical and early clinical trial simulation and modeling analysis available today."

### Jeff Poulton Appointed Shire Chief Financial Officer and Joins Board of Director

*Shire plc, 30 April 2015*

Shire plc announces the appointment of Jeff Poulton as Chief Financial Officer (CFO) and member of the Executive Committee. Jeff will additionally join the Shire Board of Directors. Both appointments are effective immediately. Jeff has served as Interim CFO since December 2014, while overseeing Investor Relations. As CFO, he will remain based in Lexington. An experienced pharmaceuticals and biotechnology executive, Jeff has extensive experience across financial, commercial and strategic leadership roles. He joined Shire in 2003.

### Jacketed Reactors for Any Application from Glass Solutions

*Glass Solutions, 29 April 2015*

Glass Solutions has launched a range of jacketed reactor systems combining excellent value with reliable performance for process development, reaction optimization, or production applications. Ideal for crystallizations, process work-ups, distillations and bioreactions, Glass Solutions Reactor Systems are designed for process development labs, kilo labs and pilot plants, and can be used in a diverse array of scientific disciplines, from the pharma and fine chemical industries to the flavor and fragrance, petrochemistry, and agrochemistry sectors.

### Karolinska Development's Annual Report 2014 Has Been Published

*Karolinska Development AB, 28 April 2015*

Karolinska Development AB announces the publication of the Annual Report 2014. The report is now available on www.karolinskadevelopment.com.

### GW Pharmaceuticals plc Announces US Patent Allowance for Use of CBDV in Treating Epilepsy

*GW Pharmaceuticals plc, 27 April 2015*

GW Pharmaceuticals plc announced today that the US Patent and Trademark Office has issued a Notice of Allowance for US Application Serial Number 13/075,873, a patent application which covers the use of cannabidivarin (CBDV) for treating epilepsy. The subject patent claims cover CBDV, a non-psychoactive cannabinoid extracted from the cannabis plant, for use in the treatment of patients with epilepsy and specifically for the control of generalised or temporal lobe seizures. This patent covers CBDV alone or in combination with standard anti-epileptic drugs. The issued patent from this application will provide an exclusivity period until 30 March 2031.


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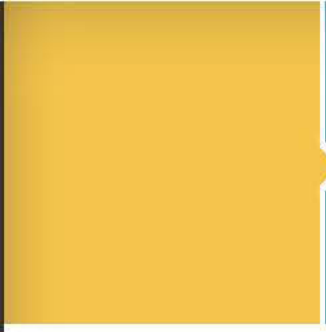

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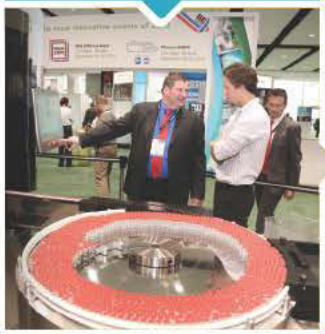

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### Bosch Packaging Technology Presents the New Granulation Unit GranuLean

*Bosch Packaging Technology, 23 April 2015*

Bosch Packaging Technology presents the new granulation unit GranuLean for the first time. Developed by the Bosch subsidiary Hüttlin GmbH, it combines the process steps of mixing, granulating and drying for the manufacturing of pharmaceutical granules. "The name GranuLean stands for a lean and compact machine, which can be easily integrated into production rooms and focuses on the basic requirements of pharmaceutical producers," Fritz-Martin Scholz, product manager at Bosch Packaging Technology, explains.

### DuPont Acquires Taxon Biosciences, Inc.

*Dupont, 22 April 2015*

DuPont announced it has agreed to acquire Taxon Biosciences, Inc., a leading microbiome discovery company. This acquisition will build on DuPont's in-house capabilities and unparalleled market access in both seed and crop protection to discover and commercialize biological solutions for agriculture customers globally.

### Quotient Clinical Completes Innovative First-In-Human Program

*Quotient Clinical, 22 April 2015*

Quotient Clinical, the Translational Pharmaceutics® Company, has announced the publication of results from an Enabled-First-in-Human (Enabled-FIH) program conducted for the Janssen WAVE Early Development unit. The integrated pharmaceutical development and first-in-human clinical program was designed to develop an optimal oral formulation, in parallel with the assessment of single and multiple dose safety, pharmacokinetics and pharmacodynamics of a highly selective small molecule c-Met tyrosine kinase inhibitor.

### Honeywell Process Solutions Launches First Digital Dashboard Monitor, Measure and Manage Cyber Security Risk

*Honeywell Process Solutions, 21 April 2015*

Honeywell Process Solutions today launched the first digital dashboard designed to proactively monitor, measure and manage cyber security risk for control systems for refineries, power plants and other automated production sites throughout the world that are at increasing risk of cyberattacks.

### New Customized Fluid Transfer Service Simplifies the Biopharmaceutical Manufacturing Process

*Thermo Fisher Scientific, 21 April 2015*

Today's manufacturers searching to simplify their supply chains and sharpen their production capabilities can benefit from a new fluid transfer service specifically for aseptic biopharmaceutical production. The Thermo Scientific Customized Fluid Transfer Service provides pre-sterilized and ready-to-use consumables tailored for a customer's facility needs, freeing up the manu-

facturer's time to focus on critical operations while optimizing cleanroom usage.

**Syrris Atlas Calorimeter Benefits Scale-Up Process**

*Syrris Limited, 21 April 2015*

A Syrris Atlas Calorimeter is proving advantageous to the Kyushu works manufacturing technology department of Nippon Steel & Sumikin Chemical Co., Ltd. in Japan, aiding scale-up of new product processes. Mr. Kenji Umeda from the Production & Technical Department explained: "Our department performs mass production studies for new product development, supporting the company's business of manufacturing coal tar, basic and fine chemicals. During product development, we undertake a series of processes from small-scale laboratory studies through to large-scale production. To ensure safe practices, we need to acquire calorimetric data during process scale-up and, after looking at various products, chose the Atlas Calorimeter with optional Atlas Syringe Pump for its accuracy and ease of use."

**ValSource Names Jeffrey L. Hartman Senior Validation and QRM Consultant**

*Valsource, April 20, 2015,*

ValSource, LLC announced, Jeffrey L. Hartman has joined North America's largest independent validation services company as a Senior Validation and Quality Risk Management Consultant. Prior to ValSource, Jeff Hartman spent 34 years with Merck, most recently serving as Director of Validation Quality Systems for Merck Manufacturing Division.

**Scientific Systems, Inc. Has Recently Launched Their Next Generation Product Line Including Includes Seven New Classes of Pumps**

*Scientific Systems, 16 April 2015*

Scientific Systems, Inc. has recently launched their Next Generation Product Line, which includes seven new classes of pumps. Described here is the LS Class, consisting of reliable single-headed, positive displacement piston pumps with very low pulsation and high accuracy. With micro-stepping motor technology and a proven single-piston pump mechanism, the LS Class exceeds the performance of more expensive units at a fraction of the cost.

**Atlas Genetics Enters into Diagnostic Collaboration with a Major Pharmaceutical Company**

*Atlas Genetics Ltd., 15 April 2015*

Atlas Genetics Ltd ("Atlas Genetics" or the "Company"), the ultra-rapid 'test and treat' molecular diagnostics company, today announces that it has entered into a collaboration with a major pharmaceutical company to develop a diagnostic test, expanding capabilities beyond infectious diseases. The io® system is a highly novel molecular diagnostic system developed initially for the ultra-rapid diagnosis of a broad range of infectious diseases. It is based on a patent-protected electrochemical sensor technology that combines speed, accuracy and low manufacturing costs.

**Watson-Marlow Fluid Technology Group Strengthens its Biopharmaceutical Offering Through the Acquisition of ASEPCO® Corporation**

*Watson-Marlow Fluid Technology Group, 9 April 2015*

Watson-Marlow Fluid Technology Group, the world leader in niche peristaltic pumps and associated fluid path technologies, has acquired Asepco through its parent company Spirax-Sarco Engineering plc, for £7.0 million. Asepco, based in California USA, specialises in the design and manufacture of high purity aseptic valves and magnetic mixers for the bioprocessing industry.

**Yokogawa Solution Service and Tokyo Electron to Jointly Develop Quality Management System for Stem Cell Production**

*Yokogawa Solution Service Corporation, 10 April 2015*

Yokogawa Solution Service Corporation announces that it will join the Smart Cell Processing project, a joint undertaking of industrial, administrative, and academic organisations in Japan and the UK that is being led by Tokyo Electron Limited, and will work with Tokyo Electron to develop a total quality management system for the automated production of stem cells that will be used in regenerative medicine.

**Optio Labs Announces the Acquisition of Oculis Labs, and Names Oculis Founder, Dr. Bill Anderson, as Chief Product Officer**

*Optio Labs, 8 April 2015*

Optio Labs, which creates technology products that make mobile devices more secure, announced that it has purchased Maryland-based security company Oculis Labs, and its CEO, Dr. Bill Anderson, will be joining the company as Chief Product Officer. Oculis is developer of the award-winning products PrivateEye and Chameleon.

**Eriez® Xtreme® Pharmaceutical Metal Detectors Remove Minute Pieces of Ferrous, Nonferrous and Stainless Steel Contaminants**

*Eriez®, 7 April 2015*

Eriez® Xtreme® Pharmaceutical Metal Detectors are designed to inspect tablets and capsules that are gravity-fed from the tablet press. These highly sensitive units remove minute pieces of ferrous, nonferrous and stainless steel contaminants, meet stringent US Food and Drug Administration (FDA) requirements and accommodate space-restricted areas within tablet and encapsulation rooms.

**New FieldMate™ R3.01 Device Management Tool Runs on Tablets**

*Yokogawa Europe B.V., 2 April 2015*

FieldMate™ R3.01.10 is the latest version of Yokogawa's multi-lingual stand-alone device management tool for configuring, maintaining and managing field devices in industrial plants. With a user interface designed for use on tablet PCs, FieldMate™ supports EDDL and FDT device integration

concepts and incorporates integrated communication paths for process automation protocols including HART, FOUNDATION™ fieldbus, PROFIBUS, Modbus and ISA100.11a wireless, as well as for Yokogawa's proprietary protocol BRAIN.

### Eriez® Appoints New Executive Vice President of Global Strategy & Development

*Eriez®, 26 March 2015*

Eriez® President and CEO Tim Shuttleworth announced the appointment of Lukas Guenthardt as Executive Vice President of Global Strategy & Development. Guenthardt recently joined Eriez in anticipation of Andy Lewis' retirement from the role of Vice President-International on 10 April 2015, according to Shuttleworth. Lewis will continue on as Chairman of the Board for Eriez-Europe. "Lukas has many years of business management experience with large and respected industrial companies," says Shuttleworth. "We are pleased that he will now apply his global skills and expertise to help Eriez maintain and expand its worldwide leadership position across the diverse industries we serve."

### Automated Packaging Systems Introduces New, Next Generation Bagger

*Automated Packaging Systems, 22 March 2015*

Automated Packaging Systems, the inventor of bag-on-roll technology and world leader in bag packaging systems, has introduced an all new, next generation bagger. The new Autobag 850S incorporates advanced sensor technology and unique versatility to accommodate a wide range of bag sizes up to 22 inches wide (2 inches wider than any other bagger). This new bag packaging system offers high-productivity bagging with an inline thermal imprinter for 1:1 personalized mail order fulfillment applications.

### Tekni-Plex Announces New Lamination Film Production Line for BarrierPharma/Medical Blister Applications

*Tekni-Plex, 19 March 2015*

Tekni-Films, a division of Tekni-Plex, Inc., is announcing a new, state-of-the-art laminated barrier films line in Holland, Ohio. Production is scheduled to begin mid-summer, with additional capabilities in the planning stages. Initially, the line will be producing high barrier, polyvinyl chloride/Aclar® laminations used to create blisters for pharmaceutical and medical device packaging applications. Additional material types are expected to follow. Tekni-Films' new capability includes high-speed manufacturing equipment, vision systems and other quality control upgrades. These conform to cGMP and ISO standards which will help customers meet their stringent productivity and regulatory requirements.

# USING CONTROL CHARTS TO EVALUATE PHARMACEUTICAL MANUFACTURING PROCESS VARIABILITY

*Daniel Y. Peng, Robert Lionberger, Alex Viehmann, Karthik Iyer and Lawrence X. Yu*

This article presents the discussion on the use of control charts to evaluate pharmaceutical process variability.

***The views presented in this article by the authors do not necessarily reflect those of the US Food and Drug Administration.***

**Abstract**

*A control chart is a graphical display of a product quality characteristic that has been measured or computed periodically from a process at a defined frequency. Control charts were developed by Walter Shewhart in 1920s and are still widely used in various industries. In this paper, we discuss the use of control charts to evaluate pharmaceutical manufacturing process variability. We first discuss different types of control charts followed by some key considerations for constructing a control chart for pharmaceutical manufacturing processes. We also share several illustrative case studies where both variable (continuous numeric data) control charts and attribute (categorical data or discrete numeric data) control charts are utilized to monitor pharmaceutical manufacturing process variation. Control charts are effective tools to detect the presence of special cause variation in the manufacturing process and to ascertain if the process has reached a state of statistical control. Control charts are also useful tools to monitor the routine commercial production and to continually confirm the state of statistical control. When the control chart detects the presence of special cause variation, continual improvements can be initiated to correct and/or prevent potential failures so that the process remains in a state of statistical control and ensure the product consistently complies with the regulatory standards. In turn, this can greatly facilitate transforming the pharmaceutical manufacture from the reactive troubleshooting paradigm to a proactive failure reduction or prevention paradigm.*

**In an ideal manufacturing world, any units produced from the production line would turn out perfectly without any deviation from the desired target and zero variability.** In reality, a certain amount of variability will exist in all process outputs regardless of how well the process is designed or maintained. A process operating with only common cause variability is said to be "in a state of statistical control" (stable state). Common cause variability is inherent to the process itself (process noise) and is random, always present and hence predictable within statistical limits. Eliminating this type of inherent variability is very difficult, if not impossible.[1] On the other hand, special cause variability is generally exterior to the process and is non-random, intermittent and not always present. When a process is under influence of special causes, it often manifests with changes in the output level, such as a spike, shift, drift, or non-random distribution of the output, i.e. the process is "out of control".[1] Special causes are usually easier to be detected, controlled and or eliminated than common causes. Due to this fact, it is cost effective to identify and eliminate special causes so that the process variability is reduced to its inherent level.

A control chart is a graphical display of a product quality characteristic that has been measured or computed periodically from a process at a defined frequency. Every control chart consists of:

- A set of chronologically plotted data points that correspond to the characteristic of interest during production
- A central line (CL) representing an estimate of the process mean or process standard deviation or other statistics
- Two horizontal lines, one on either side of the central line, called the upper control limit (UCL) and the lower control limit (LCL), which are the thresholds at which the process output is considered statistically "unlikely" and are drawn typically at three standard deviations from the center line

Control charts were developed by Walter Shewhart in 1920s[2] and are still widely used in many industry segments for example automobile, electronic devices, chemical and pharmaceutical industries.[2-9] Based on the underlying statistical principles, control chart is an efficient tool to detect the presence of special cause variation in the manufacturing process and to ascertain if the process has reached a state of statistical control. When the control chart detects the presence of a special causes, other Statistical Process Control (SPC) tools such as flow charts, brainstorming, cause-and-effect diagrams, or Pareto analysis can be used to identify the special causes. Special causes, when identified, are either controlled or eliminated and hence the product quality is improved through reducing variation. When all special causes have been eliminated and there are no detectable patterns or trends in the process output characteristics and only the common cause

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| Table A | Control limits for MR, R and S charts | | |
|---|---|---|---|
| | **MR Chart** | **R Chart** | **S Chart** |
| Subgroup Size | n = 1 | 2 ≤ n ≤ 10 | N > 10 |
| Test Statistics | $MR_i = \lvert X_i - X_{i-1} \rvert$ | $R_i = X_i^{\max} - X_i^{\min}$ | $S_i = \sqrt{\frac{\sum_{i=1}^{n}(X_i - \overline{X})^2}{(n-1)}}$ |
| CL | $\overline{MR} = (MR_1 + MR_2 + ... + MR_{k-1})/(k-1)$ | $\overline{R} = (R_1 + R_2 + ... + R_k)/k$ | $\overline{S} = (S_1 + S_2 + ... + S_k)/k$ |
| Estimated Inherent Variability ($\hat{\sigma}$) | $\hat{\sigma} = \frac{\overline{MR}}{d_2}$ | $\hat{\sigma} = \frac{\overline{R}}{d_2}$ | $\hat{\sigma} = \frac{\overline{S}}{c_4}$ |
| UCL | $D_4\overline{MR}$ | $D_4\overline{R}$ | $B_4\overline{S}$ |
| LCL | $D_3\overline{MR}$ | $D_3\overline{R}$ | $B_3\overline{S}$ |

variation exists, a process is operating in a statistical control state (stable state). Thus, the expected range of process outputs can be reliably predicted by the control charts. If the product still does not meet the customer needs (specifications) under the ideal stable state, fundamental changes to the process are necessary.

In the authors' previous papers,[11,12] we discussed how to use the process capability index as a quantitative tool to ensure drug product quality. In order to reliably forecast future batch failure rate and to evaluate if the process is capable, one of the prerequisites is to demonstrate that the process is "in a state of statistical control". In addition, it is necessary to know the inherent variability to calculate the process capability index (Cpk).[11] In practice, it is difficult to know the true value of inherent variability. Hence, within subgroup variability (also referred to as short term variability) of the control chart is often used to estimate the true value of inherent variability.[1] To address these two perspectives, in this paper, we further discuss the topics related on how to use control charts to evaluate if a process is in a state of statistical control and how to estimate the within subgroup variability. We first discuss different types of control charts followed by some key considerations for constructing a control chart. Last, we share with several illustrative examples of different type of control charts with pharmaceutical case studies. In this paper, we limit the scope to univariate control chart and assume the monitored product quality characteristics are independent of each other.

## Types of Control Charts

There are two important types of control charts, namely, the variable control chart and the attribute control chart. The variable control chart is used for product quality characteristics which are measured on a continuous scale, for example purity of drug substance, tablet hardness, dissolution, or content uniformity. Attribute control chart is used for categorical data for example, the counts of conforming or non-conforming batches, or counts of occurrences (discrete numeric data) of events in a defined interval of time or unit of space, for example the number of defective elements on a circuit board; counts of particulate matter in an injection vial; number of deviations in every 10 pages of bath record.

### *Variable Control Charts (For Continuous Numeric Data)*

When dealing with continuous numeric quality characteristic, it is usually necessary to monitor both the average of the quality characteristic and its variability. The average and variability control charts are usually prepared and analyzed in pairs. Monitoring the process average is usually done with an average chart (Xbar chart) or individual chart (I-chart). Process variability can be monitored with Moving Range chart (MR chart), Range chart (R chart), or Standard Deviation chart (S chart) depending on the subgroup size:[18]

- When subgroup size is equal to one, individual chart (I-chart) and moving range chart (MR chart) are used.
- When subgroup size is between two and 10, average chart (Xbar chart) and range chart (R-chart) are used.
- When subgroup size is greater than 10, average chart (Xbar chart) and standard deviation chart (S-chart) are used.

The calculation formula for control limits of the variability control charts (MR chart, R chart, and S chart) are summarized in Table A. The calculation formula for control limits of the I-chart and Xbar chart is summarized in Table B. Please note the control limits for I-chart and Xbar chart depend on the variability control chart used.

The formula used to estimate within subgroup variability ($\hat{\sigma}$), which is also referred to as short term variability also depends on the type of variability control chart used:

$$\hat{\sigma} = \frac{\overline{MR}}{d_2} \text{ or } \frac{\overline{R}}{d_2} \text{ or } \frac{\overline{S}}{c_4}$$

Where, MR-bar is the average moving range, R-bar is the average range, and S-bar is the average standard deviation of all subgroups; $d_2$ and $c_4$ are factors dependent on the subgroup size of the control chart. These factors can be found in many statistical quality control textbooks and relevant guideline documents.[1,14]

| Table B | Control limits for Average control chart (I chart and Xbar chart) | | |
|---|---|---|---|
| | I – MR Chart | Xbar – R Chart | Xbar – S Chart |
| Center Line | $\overline{\overline{X}}$ | $\overline{\overline{X}}$ | $\overline{\overline{X}}$ |
| UCL | $\overline{\overline{X}} + E_2\overline{MR}$ | $\overline{\overline{X}} + A_2\overline{R}$ | $\overline{\overline{X}} + A_3\overline{S}$ |
| LCL | $\overline{\overline{X}} - E_2\overline{MR}$ | $\overline{\overline{X}} - A_2\overline{R}$ | $\overline{\overline{X}} - A_3\overline{S}$ |

***Attribute Control Charts (For Categorical Data or Discrete Numeric Data)***

The attribute control chart is similar in structure to the variable control chart, except that they plot statistics from categorical data or count (discrete numeric) data (integer only). The first type attribute control chart pertains to the fraction of nonconforming product produced by a manufacturing process, namely, p chart and np chart. The second type attribute control chart is used to assess the count of occurrences of nonconformance in a defined interval of time or unit of space within which there are multiple opportunities for occurrence, namely, c chart and u chart.

The p chart is used for subgroups consisting of the fraction (proportion) of a nonconforming event, also known as the fraction occurrence of an event in the subgroup. The np charts are used for subgroups consisting of the number of occurrences in the subgroup. The pharmaceutical industry defines an "occurrence" as a nonconformance of a unit with respect to the regulatory specification. The p chart can be used for variable subgroup sizes, but the limits are calculated and plotted for each value of the subgroup size, which will result in varying (uneven) control limits for each point. The np chart can only be used when the sample size for each subgroup is constant. Under this scenario, the np chart is identical to the p chart, but the vertical scale is multiplied by the subgroup size n. For p chart, the proportion defective $p_i$ for each subgroup can be calculated by:

$$p_i = X_i / n$$

Where $X_i$ = the number of occurrences for the $i^{th}$ subgroup and n = subgroup sample size. When the subgroup size for all k subgroups is equal, the average proportion defective over all k subgroups is:

$$\overline{p} = \sum_{i=1}^{k} p_i / k = (p_1 + p_2 + ... + p_k)/k$$

When subgroup sizes differ, the average proportion defective for all k subgroups is:

$$\overline{p} = \sum_{i=1}^{k} X_i / \sum_{i=1}^{k} n_i$$

The underlying statistical principles for p chart and np chart are based on the binomial distribution. The calculation formula of the test statistics, the estimated inherent variability ($\hat{\sigma}$), the upper and lower statistical process control limits for the p chart and np chart are summarized in Table C.

The c chart and u chart are used to assess the count of occurrences of nonconformance in a defined interval of time or unit of space within which there are multiple opportunities for occurrence. The c chart can only be used when the sample size for each subgroup is constant, and u chart is used when the subgroup sizes vary.

For c chart, the number of occurrences for each subgroup is counted and the average count over all subgroups is calculated by:

$$\overline{c} = \sum_{i=1}^{k} c_i / k = (c_1 + c_2 + ... + c_k)/k$$

The c chart and u chart are based on the Poisson distribution. The calculation formula of the test statistics, the estimated inherent variability ($\hat{\sigma}$), the upper and lower control limits for c chart and u chart are also summarized in Table C.

In contrast to variable control chart (for continuous numeric data), which is normally analyzed in pairs (average and variability), in the case of attributes control chart (for categorical data or discrete numeric data), a single chart will be sufficient since the assumed distribution has only one independent parameter, the average level.

***Other Control Charts***

The main disadvantage of the traditional Shewhart control chart as discussed above is that it uses only the information about the process contained the last sample observation and it ignores any information given by the entire sequence of points. This feature makes Shewhart control chart relatively insensitive to small process shifts i.e. on the order of 1.5σ or less.[11] This potentially makes Shewhart control chart less useful for monitoring a stabilized process, where the mean and standard deviation tends to operate in control and special causes do not typically result in large process upsets or disturbance. Two very effective alternatives to Shewhart control chart can be considered when small process

shift is of interest, i.e., the cumulative sum (CUSUM) control chart [15] and exponentially weighted moving average (EWMA) control chart.[16]

***Cumulative Sum (CUSUM) Control Chart***

CUSUM control chart is a sequential analysis technique developed by E.S. Page of the University of Cambridge in 1954.[15] It is typically used to detect small process shift. As its name implies, CUSUM involves the calculation of a cumulative sum (which is what makes it "sequential") of the differences between sample values and the target.

$$C_i = \sum_{j=1}^{i} (\overline{X}_j - T)$$

Where, $T$ is the target for the process mean, $\overline{X}_j$ is the average of the jth sample, $C_i$ is the cumulative sum of the differences between sample values and the target.

*Exponentially Weighted Moving Average (EWMA) Control Chart*

First introduced by Roberts in 1959, the main idea of applying EWMA to control charting is to combine current and historical observations in such a way that small but subtle changes in the mean can be aggregated in the charting statistics so that these changes can be more rapidly detected.[16]

The EWMA chart is a useful supplementary control chart to the traditional Shewhart control charts, can be a good companion to the I-chart for individual observations. The EWMA chart reacts more quickly to smaller shifts in the process characteristic, on the order of 1.5 standard errors or less, whereas the Shewhart-based charts are more sensitive to larger shifts. The EMWA chart is also used in process adjustment schemes where the EWMA statistic is used to locate the local mean of a non-stationary process and as a forecast of the next observation from the process.[10]

## Key Considerations for Constructing a Control Chart

***Choice of Drug Product Quality Characteristics***

The selection of quality characteristics to be monitored via control charts should be the first priority of operations. Quality characteristics that could affect the performance (which is related to patient safety and efficacy) of the drug product should be considered first. In addition, product quality characteristics that can assist in furnishing information about process variability can also be included so that the process can be corrected in a timely manner. As per ICH Q8, a critical quality attribute (CQA) is a physical, chemical, biological or microbiological property or characteristic of an output material including finished drug product that should be within an appropriate limit, range, or distribution to ensure the desired product quality.[17] The identification of CQA is primarily based upon the severity of harm to the patient should the product fall outside the acceptable range for that characteristic. In general, all CQAs of the finished drug product and critical attribute of process intermediate should be monitored with a SPC program. Some users also closely monitor input material attributes and process parameters that can significantly impact the identified drug product CQAs.

***Product and Process Design and Understanding***

Drug product and process design and understanding are the key activities during pharmaceutical development. As outlined in ICH Q8, any aspect (e.g., drug substances, excipients, formulation, container closure systems, manufacturing processes, in-process material, and finished drug product) that is critical to product quality, safety and efficacy should be identified and appropriately controlled.[13] The knowledge and enhanced understanding of the product and process can greatly facilitate the selection of the most optimal place to establish controls such that any irregularities in the performance of the process can be quickly identified and prompt corrective action can be deployed. It is equally important that the analytical methods and procedures used to measure or monitored the product quality are appropriately validated or verified for its intended purpose.

**Table C** Calculation formula for attribute charts (p chart, np chart, c chart and u chart)

| | P Chart (fraction of nonconforming) | np Chart (number of nonconforming) | c Chart (count of nonconformance) | U Chart (count of nonconformance/unit) |
|---|---|---|---|---|
| Center Line | $\overline{p}$ | $n\overline{p}$ | $\overline{c}$ | $\overline{u}$ |
| Estimated Inherent Variability ($\hat{\sigma}$) | $\sqrt{\overline{p}(1-\overline{p})/n}$ | $\sqrt{n\overline{p}(1-\overline{p})}$ | $\sqrt{\overline{c}}$ | $\sqrt{\frac{\overline{u}}{n}}$ |
| UCL | $\overline{p}+3\sqrt{\overline{p}(1-\overline{p})/n}$ | $n\overline{p}+3\sqrt{n\overline{p}(1-\overline{p})}$ | $\overline{c}+3\sqrt{\overline{c}}$ | $\overline{u}+3\sqrt{\frac{\overline{u}}{n}}$ |
| LCL | $\overline{p}-3\sqrt{\overline{p}(1-\overline{p})/n}$ | $n\overline{p}-3\sqrt{n\overline{p}(1-\overline{p})}$ | $\overline{c}-3\sqrt{\overline{c}}$ | $\overline{u}-3\sqrt{\frac{\overline{u}}{n}}$ |
| Notes | If n varies, use individual $n_i$ for each subgroup | n must be a constant | n must be a constant | If n varies, use individual $n_i$ for each subgroup |

***Number of Subgroups, Subgroup Size and Sampling Frequency***

The central idea of control charts is the division of observations into "rational subgroups", within which the variations are assumed to be due to common causes only, but between which the variations are assumed to be due to special causes. Therefore, the sampling plan for collecting subgroup observations should be designed to minimize the variation of observations within a subgroup and to maximize variation between subgroups. This gives the best chance for the within-subgroup variation to estimate only the inherent process variation.[1] In most cases, pharmaceutical product manufacturing is completed in the batch mode. Therefore, each batch can be considered as a subgroup for constructing a control chart to evaluate between batch variability. If within batch variability is of the interest for monitoring, similar rational subgroup principles can be used to decide the sampling plan during a large production batch manufacturing. A similar approach can also be used to develop appropriate sampling plans to monitor process variability for continuous manufacturing runs.

The underlying statistical calculation for control charts are based on sample size and therefore subject to sampling error. Generally, the larger the sample size, the more accurate the sample estimates will be. ISO 8528 suggests that it is preferable to have at least 25 subgroups to evaluate if a process has reached a stable state (in statistical control).[9] ASTM E2587 recommends at least 100 numeric data points be collected if subgroup size > 1, or at least 30 data points be collected for single observations per subgroup. For attribute data (categorical data or discrete numeric data), a total of 20 to 25 subgroups of data are suggested.[1] Many scientists also use 30 as a cutoff because this number seems to be large enough that the central limit theorem and law of large numbers can come into effect. Nevertheless, pharmaceutical scientists should use discretion in selecting the number of subgroups to ensure the intended objective is achieved. For example, during process scale up and qualification stage, data are collected to evaluate if the process has reached the stable state. For this purpose, higher level of sampling and additional testing may be valuable. The authors shared a theoretical example of "staged sampling approach" when limited batches have been manufactured during process performance qualification (PPQ) stage in our previous paper.[11] On the other hand, during routine commercial manufacturing, a less rigorous sampling plan is sufficient if the process has achieved a stable state (in a state of statistical control).

In designing a control chart, we also need to specify sampling frequency. The size of the subgroup and sampling frequency is generally determined by practical considerations, such as time and cost of an observation, the process dynamics (how quickly the output responds to upsets), and consequences of not reacting promptly to a process upset.[1] For instance, large subgroups taken at less frequent intervals may detect a small shift in the process average more accurately, but small subgroups taken at more frequent intervals will detect a large shift more quickly. It should be noted that sampling at too high of a frequency (for example taking hundreds of samples from a single batch) may introduce correlations between successive subgroups (also known as autocorrelation) and may violate the randomness assumption in determining if a process is in a state of statistical control.

Another way to evaluate the decision regarding sample size and sampling frequency is through the average run length (ARL) of the control charts. Essentially, ARL is the average number of points that must be plotted before a point indicates an out-of-control condition.[10] A long ARL is desirable for a process located at its specified level (so as to minimize calling for unneeded investigation or corrective action) and a short ARL is desirable for a process shifted to some undesirable level (so that corrective action need to be called for promptly).[10]

***Establishing the Statistical Process Control Limits for Control Chart***

The upper and lower statistical process control limits (UCL and LCL) are the thresholds at which the process output is considered statistically 'unlikely' and are drawn typically at three standard deviations from the center line. These limits were chosen by Shewhart to balance the two risks of: 1) failing to signal the presence of a special cause when one occurs; 2) occurrence of an out-of-control signal when the process is actually in a state of statistical control (a false alarm).[1]

There are two distinctively different stages to establish and use the control limits. Within the context of pharmaceutical manufacturing, the first stage to establish the statistical process control limits often happens during process validation Stage 2 (Process Qualification).[18] Data obtained from the initial commercial manufacture process, for example technology transfer batches, engineering trial batches and process performance qualification (PPQ) batches, are collected and plotted on control charts. Trial control limits are calculated in a retrospective way to assess the current state of the process. If any points are outside the trial control limits, these batches are investigated to identify any special causes such as raw material variability, batch size change, equipment design and principle changes, commercial site facility and utilities changes. The control strategy established during process development stage (Stage 1) is then revised in an effort to eliminate or mitigate these identified special causes. Then, these points outside the control limits are excluded and the control limits are revised. The remaining data points are re-examined using the revised control limits. This type of analysis may require several cycles, and eventually reliable control limits are established. It is noteworthy to mention that the exclusion of subgroups representing "out of statistical control" is not to "throw away bad data". Rather, by excluding the points affected by known special causes, the control chart has a better chance to estimate the inherent variability of the process. In turn, the established control limits can reliably detect occurrences of any special cause variation in future routine commercial manufacturing.

Once the process has reached a stable state and the desired product quality has been achieved (a capable process), the process is ready to move into routine commercial manufacture stage (process validation Stage 3 – continued process verification).[18]

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The established statistical process control limits are then used to monitor the routine commercial manufacturing and to continually confirm the state of statistical control. When the control chart detects new special causes entering the system or the reoccurrence of previous special causes, a continual improvement strategy can be initiated to correct and prevent potential failures so that the process remains in control. If the established control limits truly reflects the inherent variability of the process, frequent revision of the control limits during Stage 3 (continued process verification) is discouraged. Nonetheless, theses control limits need to be updated when significant process changes have occurred.

It is crucial to understand the difference between the statistical process control limits of control chart and specification limits (acceptance criteria) of the finished drug product. According to ICH Q6A: Specification is a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.[19] Basically, specification limits pertain to patients' needs (product safety and efficacy), while control limits refer to the voice of process (the observed variability in the data). The statistical process control limits in the control chart provide an indication of impending problems and allow operating personnel or process engineers to take corrective action before any out of specification products are actually produced. In turn, this can transform the pharmaceutical manufacturing from the reactive troubleshooting paradigm to a proactive failure reduction or prevention paradigm.[7,20]

## Interpreting Control Charts

The function of the control chart is to provide a statistical signal when special causes of variations are present in the process. The detection of special cause is achieved by using the so-called 8 Western Electric Rules.[1,9,21] The most commonly used rule (Rule No.1) is that if any point falls outside either control limit, the process is considered as "out of control". For variable control charts (prepared in pairs-average and variability control chat), the variability control chart (Moving Range, Range, or Standard deviation control chart) evaluation is conducted first since the control limit in the process average control chart (Xbar chart) is based on the variability control chart. When the variability chart is out of control, this means the process variability is unstable. Thus, the calculated control limits for average chart is not reliable. Only when both variability chart and process average chart (Xbar chart) are in control, the process is in statistical control for the monitored quality characteristics.

Special cause variation may also be indicated by certain nonrandom patterns of the plotted subgroup statistic, which pertains to other Western Electric rules. These rules should be used judiciously since they can increase the risk of a false alarm, in which the control chart indicates lack of statistical control when only common cause variability is observed. For a complete discussion of these rules, please see other references.[1,9,10,17]

It is noteworthy to mention that a control chart is used to evaluate if a process is in a state of statistical control (predictable in a statistical sense). Control charts do not indicate how large or small the variability and the location of the average are in relation to the specification limits (acceptance criteria). A process can be very stable but not meet customer needs (out of specification limits, i.e. not capable). Vice versa, a process may not be stable yet; however, the quality characteristics are still well within the specification limits. Process capability index (Cpk) links these two perspectives (stable and capable) together, detailed discussion can be found in our previous papers.[11,12]

## Illustrative Examples

### *1. Variable Control Chart for Multiple Continuous Numeric Measurements (Xbar-R Chart)*

Table D shows the tablet Assay data of 25 batches of Acyclovir tablets manufactured by Ranbaxy Laboratories Ltd. (Dewas, M.P., India). The raw data is obtained from literature[22] and the first 25 batches were used to calculate the control limits and construct the control chart which is used to evaluate if the process is in a statistical control state, and to estimate the inherent process variability based on the within subgroup variability. The software used is Minitab 16 (version 16.2.2.0, Minitab Inc., State College, Pennsylvania). (Note: FDA does not endorse any particular software vendors.) Assay data were obtained at beginning, middle and end of the compression run (the subgroup size is 3), hence, Assay average and Range chart (Xbar – R) chart is constructed for this case study. The Range which is the absolute difference between the maximum and minimum values in each subgroup is calculated and presented in Table D. The average Assay (X-bar) of each subgroup, the grand average of all Assay data (X-double bar = 100.287) and the average range (R-bar = 1.78) of the first 25 batches are also presented in Table D.

The control limits related to the Range-chart were calculated using the formulas presented in Table A.

$$UCL = D_4 \bar{R}$$

$$LCL = D_3 \bar{R}$$

In this case, D3 = 0.000 and D4 = 2.574 for a subgroup size of 3. So, LCL is 0 and UCL is 4.582 for the Range chart.

The control limits related to the Assay average (Xbar) chart were calculated using the formulas presented in Table B.

$$UCL = \bar{\bar{X}} + A_2 \bar{R}$$

$$LCL = \bar{\bar{X}} - A_2 \bar{R}$$

In this case, the value of $A_2$ = 1.023 for a subgroup size of 3. R-bar is obtained from the Range chart (1.78) and the calculated LCL and UCL for Xbar chart are 98.466 and 102.108, respectively.

Figure 1 displays the process capability analysis summary (Xbar-Range chart, run chart, histogram, normality assessment, and capability plot). The Xbar-Range chart does not reveal any special cause variation which indicates that statistical control state has been achieved. The within subgroup variability (R-bar/$d_2$ = 1.051) and process capability indices (Cp and Cpk) are displayed on the capability plot.

### *2. Variable Control Chart for Single Continuous Numeric Measurement (I -MR charts)*

In most cases, pharmaceutical products are manufactured in batch mode which means only one value is reported for each quality characteristic of a batch (e.g. batch release data for Assay, Content Uniformity, Dissolution, etc.). To address this issue, the individual chart (I-chart) and moving range chart (MR chart) can be used. An illustrative example is given here. Product X (tablets) content uniformity (CU) data (the Acceptance Values, AVs) for the last 30 commercial batches manufactured by Firm Y is presented in Table E. The acceptance value is calculated based on USP <905> (Uniformity of Dosage Units).[23] The specification limit is AV < 15. Since each batch contains only 1 acceptance value (AV), the I-MR charts are plotted.

The moving range is the absolute difference between successive pairs of measurements. The calculated moving range between successive pairs of measurements, average moving range (MR-bar = 0.910) and the average of all AV for last 30 commercial batches (Xbar = 3.137) are also presented in Table E. Figure 2 displays the process capability analysis summary (I-MR chart, run chart, histogram, normality assessment, and capability plot).

The UCL and LCL in the Moving Range chart were calculated using the formula presented in Table A.

$$UCL = D_4 \overline{MR}$$

$$LCL = D_3 \overline{MR}$$

In this case, for the moving range span of 2, D3 = 0.000 and $D_4$ = 3.267. Therefore, LCL = 0 and UCL = 2.974. Observations 42 and 43 failed the special cause test 1 because it is beyond the UCL of the Moving Range chart.

The UCL and LCL related to the Individual Chart were calculated using the formula presented in Table B.

$$UCL = \overline{\overline{X}} + E_2 \overline{MR}$$

$$LCL = \overline{\overline{X}} - E_2 \overline{MR}$$

In this case, MR-bar is 0.910 as shown in Moving Range chart. $E_2$ is calculated based on d2 ($E_2$ = 3/$d_2$). For the moving range span of 2, $d_2$ = 1.128, $E_2$ is equal to 2.659. Therefore, LCL = 0.716 and UCL = 5.558 for the Individual chart. Observation 43 failed the special cause test 1 because it is beyond the UCL of the Individual chart.

**Table D** Tablet Assay Data for 25 Batches of Acyclovir Tablets Manufactured by Ranbaxy Laboratories Ltd. (Dewas, M.P., India); Raw Data is Obtained from Reference 18 (Subgroup size = 3)

| Batch No. | Assay Value in Percent (subgroups) | | | Average of Subgroup (S1 + S2 + S3)/3 | Range of Subgroup (Maximum Value – Minimum Value) |
|---|---|---|---|---|---|
| | S1 | S2 | S3 | | |
| 1 | 100.3 | 99.3 | 100.0 | 99.867 | 1.0 |
| 2 | 100.0 | 101.8 | 101.4 | 101.067 | 1.8 |
| 3 | 100.0 | 100.9 | 101.3 | 100.733 | 1.3 |
| 4 | 101.4 | 100.7 | 102.3 | 101.467 | 1.6 |
| 5 | 101.3 | 100.9 | 99.2 | 100.467 | 2.1 |
| 6 | 102.3 | 100.6 | 98.6 | 100.500 | 3.7 |
| 7 | 97.0 | 100.0 | 100.8 | 99.267 | 3.8 |
| 8 | 99.0 | 100.7 | 99.8 | 99.833 | 1.7 |
| 9 | 102.3 | 100.1 | 99.8 | 100.733 | 2.5 |
| 10 | 99.2 | 100.1 | 100.2 | 99.833 | 1.0 |
| 11 | 98.6 | 99.6 | 99.7 | 99.300 | 1.1 |
| 12 | 100.8 | 99.6 | 99.3 | 99.900 | 1.5 |
| 13 | 99.8 | 100.3 | 101.8 | 100.633 | 2.0 |
| 14 | 99.8 | 100.0 | 99.3 | 99.700 | 0.7 |
| 15 | 100.2 | 100.0 | 101.8 | 100.667 | 1.8 |
| 16 | 99.7 | 101.4 | 100.9 | 100.667 | 1.7 |
| 17 | 99.3 | 101.3 | 100.7 | 100.433 | 2.0 |
| 18 | 101.8 | 102.3 | 100.9 | 101.667 | 1.4 |
| 19 | 100.9 | 97.0 | 100.6 | 99.500 | 3.9 |
| 20 | 100.7 | 99.0 | 100.0 | 99.900 | 1.7 |
| 21 | 100.9 | 102.3 | 100.7 | 101.300 | 1.6 |
| 22 | 100.6 | 99.2 | 100.1 | 99.967 | 1.4 |
| 23 | 100.0 | 98.6 | 100.1 | 99.567 | 1.5 |
| 24 | 100.7 | 100.8 | 99.6 | 100.367 | 1.2 |
| 25 | 100.1 | 99.8 | 99.6 | 99.833 | 0.5 |
| Grand Average | | | | X-double bar = 100.287 | R-bar = 1.78 |

Since the MR chart and I-chart signal the process is "out of control" (not stable), this indicates special cause variation exists for tablet content uniformity of these 30 commercial batches. However, product content uniformity is well within USP specification (AV < 15) and has a high process performance index (Ppk = 4.18) (capable). This is a situation where from a practical perspective, no further action is required using the risk-based approach.

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### *3. Attribute Control Chart for Fraction of Nonconforming (p-chart)*

The manufacture activities of a drug product manufacture site A was monitored for the last 25 months. The number of batches manufactured in each month, the number of batches that were rejected from each month, and their corresponding fractions are presented in Table F. The p chart is the appropriate chart to use here since the total and "rejected batches" of each month were counted (discrete numeric data) and the number of batches made each month varies. The average fraction of rejected batch for all 25 months is calculated using the formula below:

$$\bar{p} = \sum_{i=1}^{k} X_i / \sum_{i=1}^{k} n_i = 23/526 = 0.0437$$

The UCL and LCL related to the p chart are calculated according to the following formulas as presented in Table C:

$$LCL = \bar{p} - 3\sqrt{\bar{p}(1-\bar{p})/n}$$

$$UCL = \bar{p} + 3\sqrt{\bar{p}(1-\bar{p})/n}$$

The p chart and binomial process capability analysis results are presented in Figure 3. Since the subgroup has varying size, the control limits change at each data point.

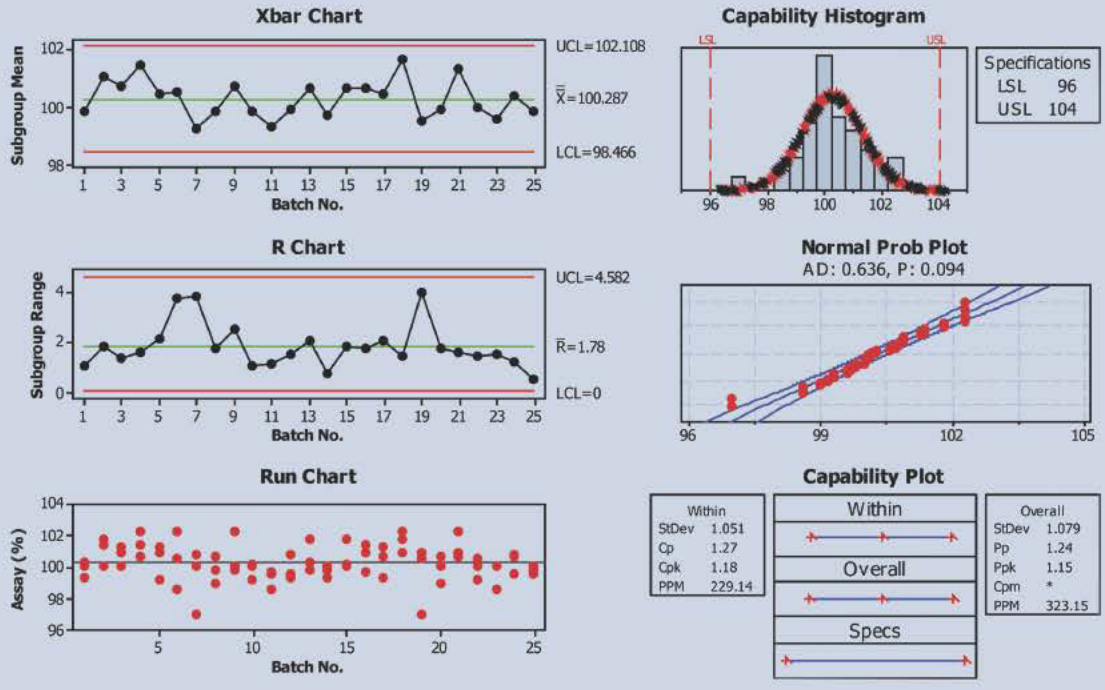
Based on the p chart, the performance at Site A is stable. The summary statistical data indicate that the average % rejected rate is 4.37%, with upper 95% confidence bound as 6.49%. The process Z-bench is 1.709, i.e. binomial process capability index is 0.57 (1.709/3) with a lower 95% confidence bound of 0.505 (1.515/3). The data indicate the process capability of Manufacture site A is poor (not capable), hence root cause analysis and continual improvements may be necessary to avert future product quality failures.

### *4. Attribute Control Chart for Count of Nonconformance (c-chart)*

Twenty five batches of 1mL injection were evaluated for particulate matter according to USP <788> (Particulate Matter in Injections).[24] The number of particulates equal to or greater than 10 microns was counted for each batch (subgroup). The c chart is utilized for this case based on its equal subgroup sizes. The counts of particulates equal to or greater than 10 micron in 1 mL injection vial are presented in Table G. The average count over all subgroups is calculated by:

$$\bar{c} = (c_1 + c_2 + ... + c_{25})/25 = 3.88$$

Figure 1 Process Capability Analysis of Tablet Assay (first 25 batches, subgroup size = 3)




Xbar, R-chart and process capability analysis of tablet Assay data of last 25 batches of Acyclovir tablets manufactured by Ranbaxy Laboratories Ltd. (Dewas, M.P., India); raw data is obtained from Reference 15 (subgroup size = 3)

The control limits, LCL and UCL, are calculated according to the following formulas as presented in Table C.

$$LCL = \bar{c} - 3\sqrt{\bar{c}} = -2.03$$

$$UCL = \bar{c} + 3\sqrt{\bar{c}} = 9.79$$

Since the calculated LCL is negative, then LCL is set to zero.

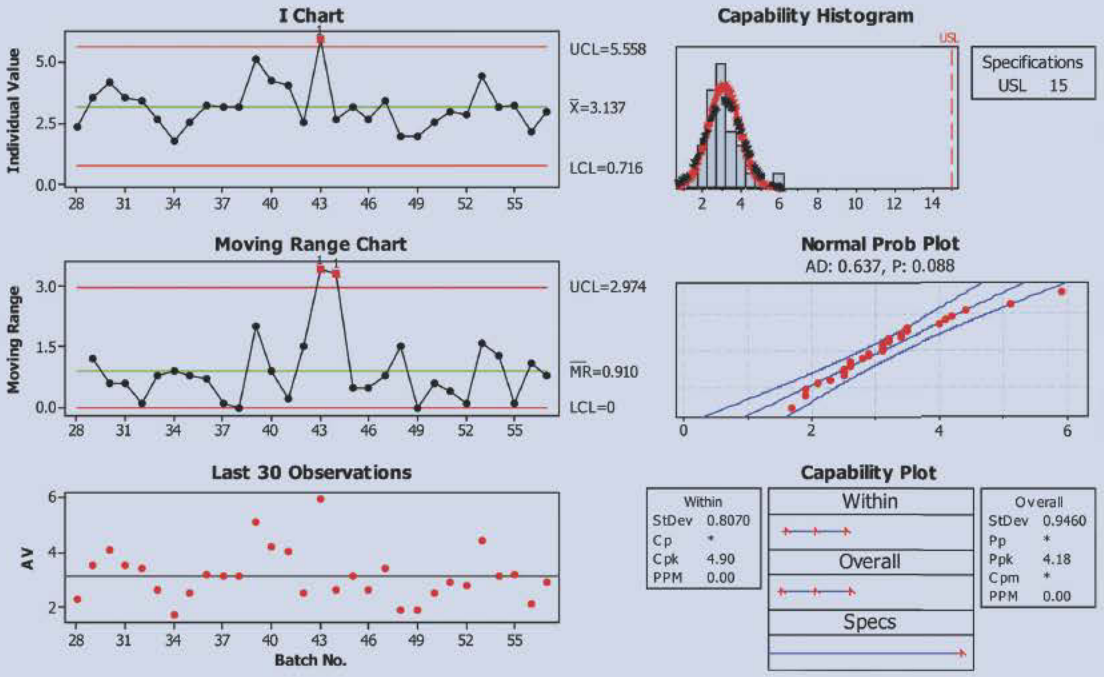
Figure 4 shows the c chart of counts of particulates equal to or greater than 10 micron in 1 mL injection vial. Based on the c-chart, the count of particulate (≥ 10 micron) is in a statistical control state.

## Summary and Regulatory Considerations

Control charts are a collection of statistical-graphical tools to detect the presence of special causes in the manufacturing process and to ascertain if the process has reached a statistical control state. Control charts are also useful tools to monitor the routine commercial production for identifying continual improvement opportunities during product lifecycle. When the control chart detects the presence of a special cause, continual improvement strategy can be initiated to correct and prevent potential failures so that the process remains in control. Control charts can be applied for both variable (continuous numeric) data and attribute (categorical data or discrete numeric) data for critical quality attributes of finished drug product, in process control of the intermediate products, incoming material attributes, and critical process parameters. The knowledge and information obtained from control charts builds a solid foundation for process capability analysis, and other statistical process control programs.

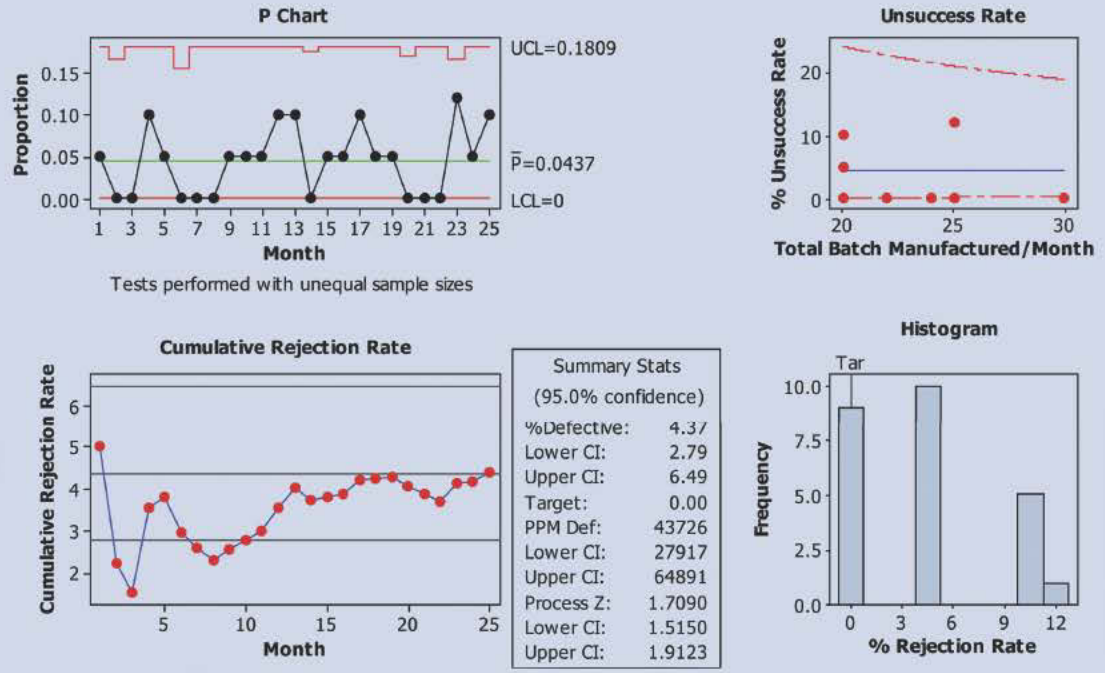
Based on these functions, it is evident that control charts are not only great tools to improve the process performance but also a valuable tool to ensure compliance with current good manufacturing practices (CGMPs) and regulations. For example, as per 21 CFR 211.180(e), it is required to maintain written records so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Another example, as per 21 CFR 211.100(a), to assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be

Figure 2 Process Capability Analysis of Tablet X Content Uniformity (AV)




I-MR chart and process capability analysis of tablet content uniformity (AV) of last 30 commercial batches of Tablet X manufactured by Firm Y (subgroup size = 1, moving range span = 2)

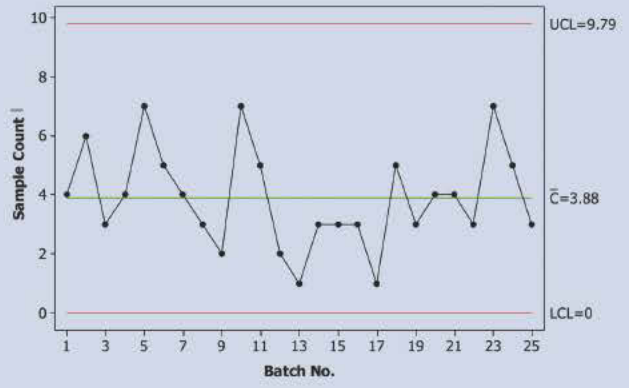
Figure 3 Binomia Process Capability Analysis of Rejected Batch




p chart of rejected batches per month at Manufactured Site A for the last 25 months (with unequal subgroup size)

responsible for causing variability in the characteristics of in-process material and the drug product. Even though it is not a requirement in the regulations to use control charts for any attribute or measurement, control chart is one tool that could satisfy these regulation requirements. As illustrated by the case studies above, the response to an "out-of-control" point (detected by the control chart) is at the drug product manufacturer's discretion, but considerations should be given based upon scientific understanding of the impact on product quality and risks to patient. In practice, many pharmaceutical companies are utilizing these SPC tools (e.g. control charts, monitoring and trending, and process capability analysis) to monitor and to improve drug product quality.[12] It would be greatly beneficial for industry to share this information with regulatory agencies to demonstrate the process is maintained at a state of statistical control and the desired process capability is achieved. In addition, the Food and Drug Administration Safety and Innovation Act (FDASIA) will allow the Agency to collect any information that would be made available on inspection.[25]

Figure 4 c chart of counts of particulates (≥ 10 micron) in 1 mL injection vial




Furthermore, there is a great need to create "Quality Culture" where the drug product manufacturers take full responsibility for the quality of their products to meet patients' needs and strive for continual improvement. By doing so, the "compliance" to regulatory expectations would just naturally follow if the focus shifts to achieve "greater performance". By invoking this type of proactive failure reduction or prevention paradigm, it will greatly facilitate the realization of "the Desired State" set forth by Dr. Janet Woodcock at the beginning of the 21st century – *"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."*[26]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| Table E | Tablet X Content Uniformity (AV) Data of Last 30 Commercial Batches Manufactured by Firm Y in 2012 | |
|---|---|---|
| **Batch No.** | **Acceptance Value (AV)** | **Moving Range** |
| 28 | 2.3 | – |
| 29 | 3.5 | 1.2 |
| 30 | 4.1 | 0.6 |
| 31 | 3.5 | 0.6 |
| 32 | 3.4 | 0.1 |
| 33 | 2.6 | 0.8 |
| 34 | 1.7 | 0.9 |
| 35 | 2.5 | 0.8 |
| 36 | 3.2 | 0.7 |
| 37 | 3.1 | 0.1 |
| 38 | 3.1 | 0.0 |
| 39 | 5.1 | 2.0 |
| 40 | 4.2 | 0.9 |
| 41 | 4.0 | 0.2 |
| 42 | 2.5 | 1.5 |
| 43 | 5.9 | 3.4 |
| 44 | 2.6 | 3.3 |
| 45 | 3.1 | 0.5 |
| 46 | 2.6 | 0.5 |
| 47 | 3.4 | 0.8 |
| 48 | 1.9 | 1.5 |
| 49 | 1.9 | 0.0 |
| 50 | 2.5 | 0.6 |
| 51 | 2.9 | 0.4 |
| 52 | 2.8 | 0.1 |
| 53 | 4.4 | 1.6 |
| 54 | 3.1 | 1.3 |
| 55 | 3.2 | 0.1 |
| 56 | 2.1 | 1.1 |
| 57 | 2.9 | 0.8 |
| Average | Xbar = 3.137 | MR-bar = 0.91 |

| Table F | Rejected Batches at Manufacture Site A and its Fraction of Each Month | | |
|---|---|---|---|
| **Month** | **Rejected Batches** | **Total Batch Manufactured** | **Fraction of Rejected Batches** |
| 1 | 1 | 20 | 0.05 |
| 2 | 0 | 25 | 0.00 |
| 3 | 0 | 20 | 0.00 |
| 4 | 2 | 20 | 0.10 |
| 5 | 1 | 20 | 0.05 |
| 6 | 0 | 30 | 0.00 |
| 7 | 0 | 20 | 0.00 |
| 8 | 0 | 20 | 0.00 |
| 9 | 1 | 20 | 0.05 |
| 10 | 1 | 20 | 0.05 |
| 11 | 1 | 20 | 0.05 |
| 12 | 2 | 20 | 0.10 |
| 13 | 2 | 20 | 0.10 |
| 14 | 0 | 22 | 0.00 |
| 15 | 1 | 20 | 0.05 |
| 16 | 1 | 20 | 0.05 |
| 17 | 2 | 20 | 0.10 |
| 18 | 1 | 20 | 0.10 |
| 19 | 1 | 20 | 0.05 |
| 20 | 0 | 24 | 0.00 |
| 21 | 0 | 20 | 0.00 |
| 22 | 0 | 20 | 0.00 |
| 23 | 3 | 25 | 0.12 |
| 24 | 1 | 20 | 0.10 |
| 25 | 2 | 20 | 0.10 |
| SUM | 23 | 526 | |

| Table G | Counts of particulates (≥ 10 micron) in 1 mL injection vials |
|---|---|
| **Batch No.** | **Counts of particulates (≥ 10 micron) in 1 mL vial** |
| 1 | 4 |
| 2 | 6 |
| 3 | 3 |
| 4 | 4 |
| 5 | 7 |
| 6 | 5 |
| 7 | 4 |
| 8 | 3 |
| 9 | 2 |
| 10 | 7 |
| 11 | 5 |
| 12 | 2 |
| 13 | 1 |
| 14 | 3 |
| 15 | 3 |
| 16 | 3 |
| 17 | 1 |
| 18 | 5 |
| 19 | 3 |
| 20 | 4 |
| 21 | 4 |
| 22 | 3 |
| 23 | 7 |
| 24 | 5 |
| 25 | 3 |

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# USING HANDHELD RAMAN SPECTROSCOPY TO REDUCE RISKS IN MATERIALS USED FOR MANUFACTURING

*Katherine A. Bakeev*

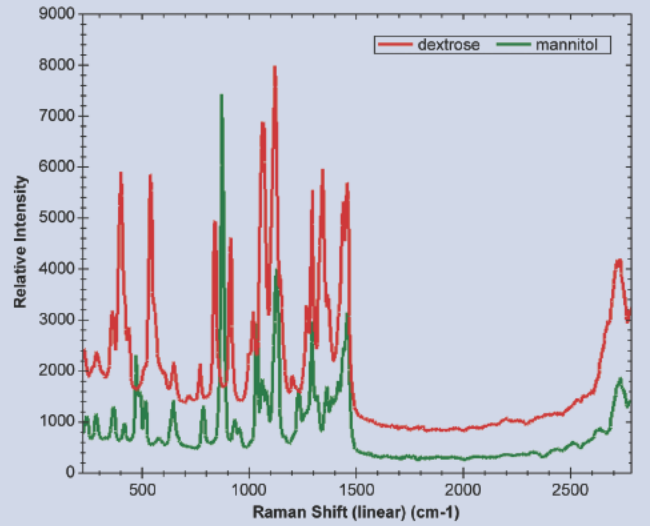
**Due to increasing competition, pharmaceutical companies are relocating their manufacturing operations overseas and sourcing raw materials from around the globe in order to help improve efficiencies and cut their production costs.** With these changes and the consolidation of the pharmaceutical industry through mergers or consolidation of resources, product quality may be negatively affected. With the risk of impacting quality, there is an increased need for tighter regulatory control to ensure safety and quality of all materials in a pharmaceutical company's production chain in order to mitigate risks; from incoming raw material to real-time monitoring during critical stages of production, and then final product inspection.

According to the ICH Q7, Good Manufacturing Practices for Active Pharmaceutical Ingredients,[1] procedures must be in place for the verification of all incoming raw materials used in production. These guidelines are now more widely adopted and have been published by PIC/S as a more globally-acknowledged GMP guide for pharmaceutical products.[2] The industry has done an excellent job of creating a strong demand for its products while striving to maintain and even improve the quality and safety to consumers. Regulatory guidance is moving towards required analysis of every container of incoming materials, which is straining the analytical capabilities of many companies and introducing unacceptable production bottlenecks and cost overruns at the manufacturing facilities. This "100% testing" is not sustainable in the long term when done using traditional laboratory testing techniques as prescribed by the monographs in the United States, European and Japanese Pharmacopoeias due to higher costs, increased manpower and additional resources required to perform more testing.[3]

In order to minimize risks in the quality and identity of raw materials, fuller testing and testing at the point of material receipt is desirable. Full testing of each received container of material can be done most cost effectively by testing methods that do not require sample preparation, and can preferably be done at the point of material receipt using portable technology. Raman spectroscopy, which can be performed with handheld instrumentation, provides a rapid, reliable means of testing in many different environments in manufacturing, including the loading dock. Raman spectroscopy is a form of molecular spectroscopy that like IR spectroscopy provides information about the structure and properties of molecules based on the vibrational transitions that occur. A Raman spectrum provides a fingerprint of a substance, as it contains information about the chemical structure and information related to the morphology (i.e. polymorphic state, crystallinity). It serves as an important tool in reducing risks in manufacturing without creating bottlenecks due to large movement of materials and many laboratory tests requiring sample preparation, as well as analysis, and reporting of results. The capability of Raman technology for rapid, nondestructive testing and identification of materials in their containers was demonstrated as early as 1998.[4] The availability of handheld Raman instruments supplied with spectral libraries has increased the adoption of Raman for such testing since they were first available in 2006. The fact that Raman technology is a nondestructive technique that requires no sample preparation, no direct contact with the sample, and has the capability to test a sample through transparent packing material such as glass or plastic has made it an ideal tool for rapid raw material identification. The adoption of this technology can also provide substantial cost savings in terms of quarantine and storage costs for materials that await testing and approval for customer use. In recent years, handheld Raman technology has gained a noticeable market in raw material identification in various industries where traditional analytical techniques like HPLC and FTIR spectroscopy have been the primary technologies. Due to the nondestructive nature of analysis which can be done through transparent packaging, operator exposure to potentially hazardous materials is minimized, as is the need to transport and re-label samples that would need to be submitted to a central laboratory for testing.[5-7]

Raman technology is accepted as a means of material identification. There are chapters for Raman spectroscopy in the US Pharmacopeia, the European Pharmacopoeia and the Pharmacopoeia of the People's Republic of China, with a new USP general chapter for Raman spectroscopy (858), currently open for

Figure 1 Overlay Raman spectra of dextrose and mannitol, two commonly used pharmaceutical excipients



comment.[8] Because handheld Raman spectrometers are available as reliable, robust instruments providing specificity in identification, their use at the point of material receipt can provide a cost-effective means of full material inspection. Handheld Raman spectrometers offer portability with an instrument providing high quality data for reliable material identification. An intuitive user interface backed by a high quality instrument with robust libraries and identification algorithms make Raman a versatile technology for use by operators and technicians. The Raman spectra of two commonly used excipients, dextrose and mannitol are given in Figure 1, illustrating the differences in a Raman spectrum for chemically similar materials such as these.

Raman spectrometers using on-board spectral libraries as well as intelligent principal component analysis (PCA) model-building software, allow for the rapid development of reliable methods for identification and verification of raw materials. Identification of an unknown compound is achieved in a very short time span (less than 30 seconds for most materials), making it a practical choice for rapid identification and verification purposes. The methodology used makes it easy to develop and validate methods since the methods can be transferred from one instrument to another. This way, the development work does not need to be repeated as more Raman instruments are deployed within a company.[5,9]

Figure 2 Identification result report for atorvastatin with overlay of sample spectrum with method reference

Scan Index: 4123 NID Client V5.12

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| **Device SN:** | SAGJMA | B NO: N/A<br>IL NO: N/A<br>Run Name: ATORVA | **Last Perf. Validation**<br>User Name: Daisy |
| **Product Name:** | ATORVASTATIN CRYST | | Date and Time: 2015/02/26 16:17:05<br>Result: Pass<br>HQI: 99.9653<br>Relative Intensity: 0.9935<br>Calibration File: ETHYL ACETATE (2015/02/26 16:16:06) |
| **Test Time:** | 2015/02/26 16:31:16 | Note: N/A | |
| **User Name:** | SPINCO | | |
| **Laser Power:** | 90% | | |
| **Integration Time:** | 1769 | | |
| **Method:** | ATORVASTATIN CRYST (2015/02/26 16:30:15) | | |
| **Significance Level:** | 0.05 | | |
| **Raman Shift Range:** | 176 (cm-1) - 2500 (cm-1) | | |
| **NOS Version:** | V5.00.06.04G | | |

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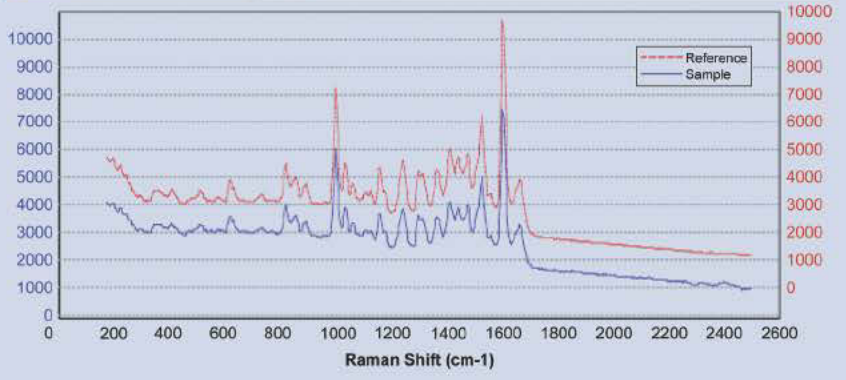
| **Result:** | Pass |
| **P-value:** | 0.9983 |




The design of handheld Raman with spectral libraries is intended to make it a tool for use where ever the analysis is needed. The systems provide rapid pass/fail results without the necessity for in-depth data analysis in a laboratory environment. The intent is to increase the testing capabilities without needing to increase the laboratory staff. A typical results report from the measurement and passing identification result for the active pharmaceutical ingredient atorvastatin is shown in Figure 2. Spectral libraries are often provided as part of commercial Raman spectrometers. Many instruments also have the capability of user-created spectral libraries, providing users flexibility in developing methods specific to their analysis needs.

The figures of merit for Raman spectrometers, says John Kauffman, Deputy Director of the FDA, Division of Pharmaceutical Analysis [E-book: Portable Raman Enters a New Era], are spectral range, resolution, signal collection times and signal-to-noise ratio. Additionally, Raman spectroscopy provides high selectivity, making it more powerful for identification than near-infrared spectroscopy. Versatility in availability of sampling accessories optimized for different sample forms makes it easy to apply Raman spectroscopy for rapid identification of samples in different packages, and in the most reproducible means.[10]

Raman spectroscopy does have limitations and cannot be used for all types of samples. Though it provides valuable information for organic as well as inorganic materials, it is not capable of analysis of metals. It is also limited in its ability to measure dark and highly colored materials which may heat up and decompose when the laser used for sample excitation interacts with them. Such samples may also have strong fluorescence, which overwhelms the Raman scattering.

User-friendliness is also an issue for handheld instruments, as the methods are most often implemented in the field by non-experts. Some instruments are designed for ruggedness, others for smallness and portability. "One encouraging development," Kauffman says, "is that vendors are improving the user interface to simplify the use of these instruments by non-experts, and some vendors are also developing chemometric tools that offer flexibility for method development scientists." [E-book: Portable Raman Enters a New Era]. The use of a touch screen with intuitive workflow provides an inviting interface for users at all levels.

In addition to identification of raw material (the first step in the manufacturing process to control) Raman spectroscopy also can reduce risk further downstream in manufacturing. Handheld

Raman can be used for the test of finished dosage forms and in the identification of counterfeits. Sometimes even the identification of products manufactured at different facilities can be identified due to the variability within the samples reflected in the Raman spectrum, and the use of PCA-based methods that provide the sensitivity to discriminate between such samples.

Considering Raman spectroscopy more broadly, it can be applied in manufacturing as a powerful tool for process analysis and control, thus contributing to the success of manufacturing quality product with an eye on the process.[11,12] Raman spectroscopy can be used for quantitative analysis as well as identification purposes. As with identification, the benefits of nondestructive, noncontact sampling with high specificity make it an excellent tool for process monitoring.

Instrumentation is part of the analytical infrastructure of companies, and having the ability to access data and results from numerous locations is important in creating uniform ways of analyzing data, and uniform means of reporting, while also being able to use information and libraries created in one site in other sites, without the need to duplicate work. The use of databases that can be stored on a server or with cloud computing, and access to those databases expand the reach of handheld Raman spectroscopy.

The IT infrastructure and data integrity and security are also important aspects of reducing risks in terms of data loss or infiltration in manufacturing. With the ability to scan barcodes and use the same sample name tracking, the risk of transcription errors is reduced. Wireless communication of handheld Raman allows field users, typically non-experts, to transmit data to a central laboratory where more in-depth analysis can be done. Likewise, wireless communication allows for easy transfer of centrally created libraries to remote users. The ability to integrate Raman data with a LIMS (laboratory information management system) system provides an additional advantage when using handheld Raman in QA applications, as it facilitates the integration of data to the full analysis of materials related to the manufacturing process. LIMS integration of Raman data and results provides a reliable means of data backup and storage within a company's framework for data management. Some handheld Raman spectrometers have the capability for LIMS integration with seamless integration with ready scripts for use with commercial LIMS systems, with defined csv file format of data and results.

Raman spectroscopy is a valuable tool to provide rapid, specific analysis for identification of raw materials, thus reducing the risk of using substandard or incorrect materials in manufacturing. The utility of handheld Raman increases productivity, and the ability to do full testing without creating bottlenecks in the production process. The integration of the Raman data into a company's data management system provides a secure means of handling data and results, with reduced risk of transcription errors, and data loss.

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## About the Author


**Dr. Katherine A. Bakeev** is the Director of Analytical Services and Support for B&W Tek in Delaware. She has many years of industrial experience in the electronics, chemical and pharmaceutical industries, with companies including GlaxoSmithKline, CAMO Software and Foss NIRSystems. Dr. Bakeev earned her PhD in Polymer Science and Engineering from the University of Massachusetts in Amherst has a Masters in Technology Management from Stevens Institute of Technology, and a BS in Macromolecular Science from Case Western Reserve University. She is the author of numerous articles and edited a book on Process Analytical Technology. She is a member of the Society of Applied Spectroscopy (SAS) since 1993, serving on the Executive Committee from 2010-2014. She serves on the Editorial Board of the journal *Applied Spectroscopy* and for *NIR News*. She is the past president of the Council for Near Infrared Spectroscopy (CNIRS), and a member of the ASTM committees E13 and E55. She can be reached by email: katherineb@bwtek.com.

# SCIENTIFIC AND REGULATORY CONSIDERATIONS FOR IMPLEMENTING MATHEMATICAL MODELS IN THE QUALITY BY DESIGN (QbD) FRAMEWORK

*Theodora Kourti, John Lepore, Lorenz Liesum, Moheb Nasr, Sharmista Chatterjee, Christine M.V. Moore and Evdokia Korakianiti*

**This article is the first of a two-part series and presents points to consider for building and using models in the regulated pharmaceutical industry and offers examples of how models can play a part in the Quality by Design (QbD) framework.**

**A model, in general, is an alternative representation of reality. A mathematical model is a description of a system using mathematical language.** Mathematical models are used extensively in process industries to describe the chemical and physical phenomena taking place during production. There are models to describe chemical reactions, crystallization, distillation, and a plethora of other operations; models that predict quality properties based on process data, i.e., soft sensors; as well as models that are used in Process Analytical Technology (PAT) applications.

The Quality by Design (QbD) framework for drug development and manufacturing is a science and risk-based approach that begins with predefined objectives for meeting the desired clinical performance and emphasizes product and process understanding and process control.[1] In the QbD framework, mathematical models can be used at every stage of product development and manufacturing. Models have been implemented in pharmaceutical industry for developing and controlling processes and have appeared in regulatory submissions.[2] Models also can be indispensable for the implementation of continuous manufacturing processes. Overall, application of models throughout a product's life cycle from development through manufacturing can enhance process and product understanding. In general, these modeling approaches are still evolving in the pharmaceutical industry.

There are many considerations in the development, validation and maintenance of models depending on their use. This article provides points to consider for the building and use of models in the regulated pharmaceutical industry. It offers examples of how models can play a part in the QbD framework, how these models can be developed, and how model information can be utilized as a part of the control strategy.

## Overview of Models

Mathematical models may be first principles or mechanistic models, empirical, or hybrid. First principles models can be derived when the underlying physical, chemical or biological phenomena are thoroughly understood and expressed in the form of equations; the Arrhenius equation and the Lambert-Beer Law are examples of first principles relationships. In addition to ample history on first principles models that appear in the science and engineering literature, there have been several publications in the literature that describe potential applications to the pharmaceutical industry,[3] including, modelling for chemical reactors, crystallization, distillation, drying, and a plethora of other unit operations in the pharmaceutical realm.

Empirical models are data based models. Depending on the objectives, different types of empirical models can be derived; the type of data required to derive such models also depend on the objectives of the model. Causal empirical models are derived from data collected from Design of Experiments (DOE); for example, models used to derive design space from DOE as well as PAT based calibration models (i.e., spectral NIR) are causal models. Other types of empirical models are those models that are derived from historical data collected on a process that may be used either for troubleshooting or for Statistical Process Control (SPC), including Multivariate Statistical Process Control (MSPC). When used for troubleshooting, all data collected over a historical period are projected on to the latent variable space to give an initial idea of clusters, outliers, unusual process periods, and other patterns to aid postulating reasons for differences. When models are used for SPC and for continued process verification, the typical operating region and control limits are well defined; historical data on good production and the typical operating region can be used for setting the limits to detect common cause variation for SPC type modelling.[19]

Hybrid models, as is evident from their name, combine theoretical knowledge with empirical data. One example of a hybrid model is presented for the design of a control strategy for control of Particle Size Distribution (PSD) in a semi-batch emulsion polymerization process.[4] A hybrid modelling approach was used for batch-to-batch optimization in which a fundamental population balance model describing PSD evolution is augmented by a Partial Least Squares (PLS) model.

The choice of the model (first principles, empirical, hybrid) depends not only on the modelling objective and the theoretical background available, but also on other criteria. For example, while there exists knowledge for detailed models for crystallization based on population balances, a DOE model based on empirical data may be chosen to be fit for purpose, based on the objective and business criteria. Finally, theoretical models can be used as directional models to aid DOE.

Models can be implemented at any stage of the product lifecycle. For the purposes of implementation, models can be classified on the basis of intended use of the model. Examples of different categories based on intended use are:

a. *Models for supporting process design:* this category of models includes, but is not limited to, models for: formulation optimization, process optimization, design space determination and scale-up.

b. *Models for supporting analytical procedures:* this category includes empirical models based on data generated by various PAT based methods; for example, a calibration model associated with a NIR based method.

c. *Models for process monitoring and control:* this category includes, but is not limited to:

- Univariate or multivariate statistical process control (SPC or MSPC) models: these models are used to detect unusual variability that is causal; the model is usually derived and the limits are determined using batches manufactured only at the target condition and producing acceptable product.
- Models used for process control (e.g., feed forward or feedback). An example is feed forward model to adjust compression settings on the basis of incoming granule material properties. An example of feedback model routinely encountered in the pharmaceutical industry is adjusting compression force on the basis of measured tablet weight.

Within each implementation mode, for the purpose of regulatory consideration, an important factor to consider is the model's contribution in assuring the quality of the product. In that context, models can be classified as high, medium or low impact:[5]

a. *High Impact Models:* a model can be considered high impact if prediction from the model is a significant determinant of quality of the product (e.g., a chemometric model for product assay, a surrogate model for dissolution).

b. *Medium Impact Models:* such models can be useful in assuring quality of the product, but are not the sole determinant of product quality (e.g., most design space models, many in-process controls).

c. *Low Impact Models:* these models are typically used to support process and product development and design efforts (e.g., formulation).

## Use of Models in a QbD Framework

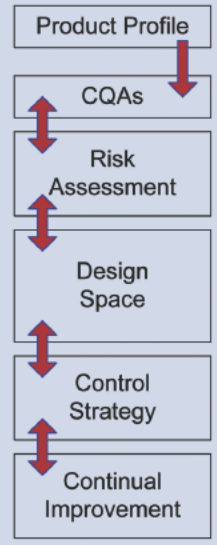
The steps in the product lifecycle in a QbD Framework are given in Figure 1. Modelling is an integral part of QbD and there can be models that are involved in every step. Examples of the types of models relevant to each step of the product's lifecycle are discussed below:

### *Establishing Critical Quality Attributes*

Once the quality target product profile is established, the next step is to define the product Critical Quality Attributes (CQAs).

*In Vivo vs. In Vitro* Correlation (IVIVC) models establish *in vitro* dissolution criteria by relating the CQA of dissolution to *in vivo* performance. IVIVC models are derived by evaluating relationships of exposure data to formulation attributes, such as disintegration or dissolution. These attributes can serve as surrogates for the various biological processes that comprise the total pharmacokinetics of a given drug product. Such modelling attempts have already been discussed in the literature.[6] A number of alternatives, such as Physiologically Based Pharmacokinetic (PBPK) models, also have been proposed.[7]

Figure 1 Modeling can be an integrated part of all stages in a QbD framework




### *Risk Assessment and Risk Mitigation*

Modeling can be a very useful tool to provide knowledge and support risk assessment and risk mitigation. Various types of models can be used for this purpose, from qualitative models that show directions of effects for a preliminary assessment to more complicated models that can be used in control strategy, as discussed later. Commercially available Computational Fluid Dynamics (CFD) software packages can be used to simulate a variety of applications, including spray drying, inhalation, mixing in agitated vessels and flow of granular material; such models may provide preliminary directional information, set strategies for DOE and then, combined with DOE, provide quantitative information that aids process understanding. As an example, CFD models may be used to understand the mixing properties of a non-traditional vessel layout and decide locations of placing sensors, such that sampling is representative of the process conditions. CFD can be used in assessing mixing sensitive chemistry to establish the role of vessel specific configurations in reaction selectivity. Other models like mass and energy balances can be used to guide DOEs.

The use of modelling to provide knowledge for mitigating risk was demonstrated in the following example.[8] The risk assessment provided a picture of the risks related to solid state form control and drying; a thermodynamic model, provided by commercially available software, was used to describe the behavior of a system, and to demonstrate that it was not thermodynamically possible to achieve an acceptable total residual water result and an unacceptable isopropanol result. Note that this model assumes no bound or trapped water in the solids. Hence, it was shown that it was possible to assure that residual isopropanol levels will meet acceptance criteria, solely by assay of the residual water content by Karl Fisher. (The risk of unacceptable isopropanol was avoided simply by controlling residual water.) The model was tested at scale using on-line dryer dew point measurements. It was concluded from the phase diagram that the thermodynamic model showed low risk of failure if the drying time was more than 3 hours for that specific equipment and by using a temperature of 45°C under vacuum conditions without specific control of humidity.

***Design Space***

A design space can be expressed as a function that relates quality to the raw material attributes and the process parameters:

*Quality = f (raw material, process parameters)*

or more specifically as:

$$[q_1,q_2, \ldots q_N] = f(z_1,z_2, \ldots z_K, x_1 1, x_1 2, \ldots x_1 M, \ldots x_N 1, x_N 2, \ldots x_N P) + Noise \quad (1)$$

When the design space is expressed in the form of equation (1) and the raw material attributes are varied, it is possible to solve for the combination of process parameters ($x_1 1, x_1 2, \ldots x_N P$) that will result in the desired set of quality attributes $q_1$, $q_2$, $q_N$ given the values of the raw input material characteristics $z_1$, $z_2$, $z_N$.[9] Notice that equation (1) can be written for one quality attribute $q_N$ or for multiple quality attributes simultaneously.

The concept of the design space is illustrated with the following simple example. In Figures 2 and 3, we have a process where the raw material is described by two attributes $z_1$ and $z_2$ (for example, for drug substance these could be particle size and density), quality is described by $q_1$ and $q_2$ (for example, dissolution and content uniformity), and unit operations described by process parameters $x_{11}$ and $x_{12}$ for unit 1 (for example, unit 1 could be high shear wet granulation, process parameters could be total water and addition time, or water and total work) and process parameters $x_{N1}$ and $x_{N2}$ for unit N (for example, main cylinder height and press speed for compression). The big circle in the "Quality" box represents acceptable quality. Two material attributes, two quality attributes, and two process parameters per unit operation are used for illustration purposes, but this does not affect the generalization of the following discussion to more variables. Each small circle represents the values of these parameters or attributes for one batch. Figure 2 shows what happens when a fixed process is considered, depicted by the red circles. Suppose that we have raw material for three batches at a selected range of (red circles) properties and we run the traditional three batches at selected range of process parameters (red circles for units 1-N) and we achieve the target quality (all red circles representing quality fall on a multivariate target). The green circles in $z_1$ - $z_2$ represent raw material from a different manufacturer and with attribute values different than the range initially examined. If we process the green material on the fixed process conditions (e.g., in the process range of the red circle values in units 1-N), there is a potential that the final quality (green circles in quality) will differ from that produced by the red raw material. Figure 3 illustrates that if we judiciously choose to operate at appropriate different process conditions for each different material (green path for the green raw material attributes and blue path for the blue raw material attributes), we can have quality on target. In other words, there is a multi-dimensional combination of raw material and process parameters that assures quality.

The model used to describe the design space may be based on first principles/mechanistic approach or may be empirical as derived from design of experiments or may be a hybrid. The choice of the type of model depends on the objective and the theoretical background available to describe the principles of the unit operations. Empirical models used to describe a design space should be causal and therefore derived from carefully designed experiments. Some DOEs also may be necessary in order to estimate parameters if mechanistic models are used. Together with the model, one has to specify the range of parameters over which the model would be expected to be valid. Therefore, in this case, the design space is the model (relationships seen by paths in Figure 3) plus the range of parameters for which the model have been verified.

A design space described with the above concept (equation (1) and paths of Figure 3) can be derived to cover a wide range of raw material characteristics and process conditions. Such an approach gives flexibility in raw materials choices, as it allows for wider choices than fixed process conditions (as seen in Figure 2). It demonstrates that for a defined set of quality values ($q_i$), a wide

Figure 2 **By maintaining fixed process conditions, it is possible to propagate raw material variability to quality.[9]**
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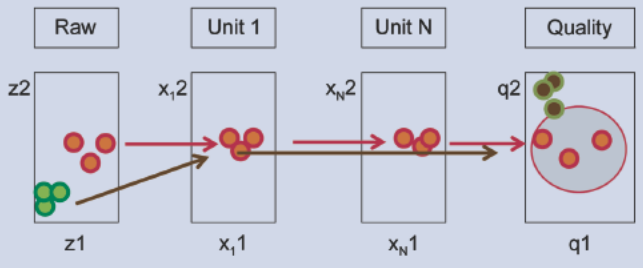


Figure 3 **By taking a feed forward approach where the process conditions are flexible to account for raw material variability, we can maintain quality on target.[9]**
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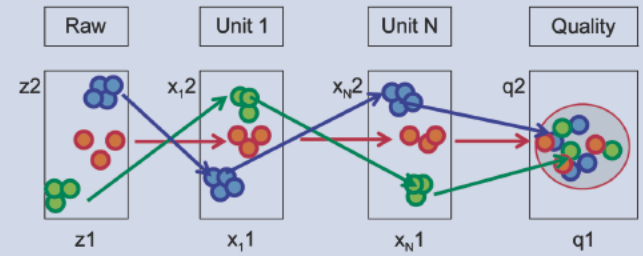
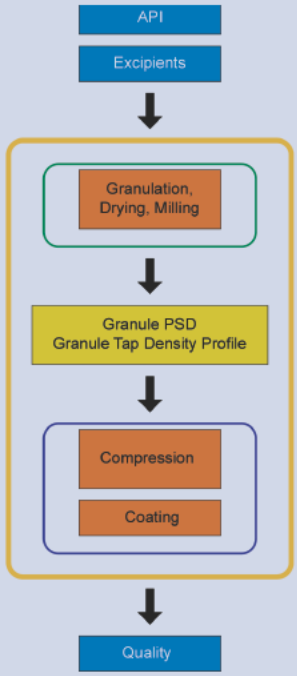


Figure 4 **Different models can be derived for tablet manufacturing**




The green frame represents model for design space of granulation which can be derived to express granule characteristics (granule PSD and granule tap density profile) as a function of the raw material (API and excipients) attributes and the granulation process parameters. Another model, represented by the blue frame, can be derived to express final quality as function of the granule characteristics (granule PSD and granule tap density profile) and the compression and coating process conditions. Finally, another model represented by the yellow frame, can be derived by expressing quality as a function of raw material (API and excipients) and process conditions from all unit operations. This yellow box represents design space for all unit operations.

range of raw material attributes can be accommodated, provided that for each combination of material attributes, specific process conditions are used (within the range that the model was tested) that satisfy the equation. It should be understood that in the presence of interaction terms or if the parameters are not orthogonal to each other, random combinations of raw material attributes and process parameters (i.e., combinations that do not satisfy equation 1) may not work.

The design space model may cover one unit operation or a series of successive unit operations. Taking the tablet manufacturing process in Figure 4 for example, one may wish to derive a model to express the granule characteristics as a function of the raw materials entering granulation and the process parameters (i.e., design space for granulation); another model may be derived to express final quality as a function of the granule characteristics and the compression and coating process conditions. Finally, another model can be derived to express quality as a function of information from all unit operations and from raw material (design space for all unit operations).

*Design Space for Multiple Unit Operations and/or Multiple Quality Attributes*

An integrated design space, established over several unit operations, provides flexibility into the choice of control actions because the type and location of the control action can be decided based on knowledge of interactions of parameters between unit operations. Problems at later unit operations can be anticipated and corrected in earlier stages. Use of an integrated design space can provide the manufacturer with the most efficient operation, that is, higher yield or lower operating costs. In other words, the control strategy and the design space are inter-dependent, such that the control strategy can be implemented in the most cost effective way.

Recognizing the continuum in drug production that spans from the drug substance to the drug product could help create a more versatile and robust design space. All the steps and materials involved in the production of the drug substance and drug product have the potential to impact the quality of the drug that will be delivered to the patient, as they were selected with the objective to achieve a desired Quality Target Product Profile (QTPP). Therefore, the final product that delivers the active pharmaceutical ingredient to a patient is indeed the result of a multidimensional combination of raw material attributes and process parameters that span several unit operations, including the drug substance production, drug product production and packaging. Each one of the unit operations may have an impact on one or more final quality characteristics or the product stability.[9] Of course, an empirical model for design space does not express each CQA as a function of every single process parameter and material attribute, because the choice of operating procedures, ranges and controls mitigate most of the risks.

As mentioned earlier, the model described in equation (1) may express the design space as multivariate model solved simultaneously for all CQAs. This approach is commonly used in other industries where a set of unit operations are described by first principles or empirical models and optimizations are solved to determine operating conditions such that the quality is assured while considering other constraints (e.g., economic, environmental) simultaneously. Multivariate expression of finished product specifications can be defined in this manner. The overall product quality expressed as the combination of all CQAs will be a function of all the material attributes and process parameters whose variability has an effect on any of the CQAs.

For empirical design space models, it is important to keep the underlying assumptions and approaches in mind. First, the potential effect of variation of those parameters that need to be controlled but were kept constant or in a narrow range during execution of the DOEs should be considered in the plans for continued process verification of the design space model. MSPC could be used to check that the ranges of these parameters are the same as those during the DOE. Additionally, if separate design space models are defined for different CQAs, the acceptable parameters and/or ranges could differ. In such cases, it is important to select design space ranges where the specifications for all the CQAs would be met simultaneously. A more comprehensive study where this was achieved by modelling all the CQAs simultaneously using advanced latent variable methods and setting multivariate specifications for the raw materials has been presented.[10]

A design space model may be linear or non-linear. In order to be able to predict intermediate quality (i.e., granule properties) as well as CQAs and also have a flexible control strategy, more than one model is typically needed for a multi-unit plant. That is, the design space for the whole process can be considered a collection of

models that: 1) relate the final quality to all previous units, raw material and intermediate quality 2) relate intermediate quality to previous unit operations and raw material and 3) predict the process conditions of the next unit operation based on the preceding intermediate quality, if feed-forward control is designed in.

*In Process Controls (IPCs) and Design Space*
Design space is an element of the overall control strategy. An IPC that is an output from one unit operation can be an input to another. When a disturbance in unit N affects the value of the output IPC of unit N, it is wise to use the value of IPC as input in unit N+1 for feed forward process control. The value of the IPC will reflect the problem created by the disturbance. For example, say in a process we have granule particle size or granule density as an IPC; we accept their values within a specific range. Knowledge when the value is close to the upper limit or lower limit of the range will give better predictability of dissolution, even if the granule density is an IPC. An example of dissolution expressed as a function of hardness or thickness (IPCs) can be found in ISPE PQLI® example.[8]

However, the design space cannot always be fully expressed with IPCs (attributes) only; the path that the process followed such that a certain attribute is achieved can be important.[11] This path is often called the "process signature."

***Control Strategy***
Various approaches to process control can be used as part of the control strategy and modelling plays a significant role in each.

It should be noted that the term "control" currently appears in the pharmaceutical literature to describe a variety of concepts such as: conformance to end product specifications, end point determination, feedback control, statistical process control, or simply process monitoring. For the purpose of this article, "process control" refers to a system of measurements and actions within a process intended to ensure desired quality output of the process.

In this section, two major approaches to process control are discussed:

- Feedback control, where corrective action is taken on the process based on measured deviations from the process output
- Feed forward control, where process conditions are adjusted based on measured deviations of the input to the process

Under the control strategy umbrella, there are a multitude of approaches that a company can take and for each approach there is a large number of modelling approaches possible to address different specific needs. Some example modelling activities are discussed below.

*Models to Support Process Analytical Technology (PAT)*
PAT can play a significant part in the control strategy by providing real time information. This information can be used for feedback or feed forward control. Empirical models are used for the data evaluation and modelling of various PAT based methods, as for example, a calibration model for a Near Infrared (NIR) based method. Commonly, chemometric models such as Principal Component Analysis (PCA) or Partial Least Squares (PLS) are used. In some cases, NIR models serve as surrogates for a primary reference method; for example, an HPLC assessment of content uniformity can be replaced by a representative NIR method. Notice that NIR based methods may use different types of models depending on the objective of the PAT application. For example, NIR can be used for water content determination utilizing PLS calibration models during a drying operation. NIR can be used for end point determination of blending utilizing rate change models;[12] but also NIR can be used for end point determination of blending by predicting the API content of the blend. Approaches for the development and validation of the model would depend on the impact of the model.

Information obtained from real time analyzers may be included in the design space, where we may have a combination of such real time values with the mechanistic or empirical model of the unit operation. For example, a model that predicts the effect of water content of granules on impurity level at release and on the shelf-life can serve to calculate constraints for the granulation design space, but also alert of a potential problem in the shelf life if atypical water content values are measured by PAT.

*Soft Sensors Models*
Soft sensor models are predictive models where the value of a quality variable is not directly measured, but is inferred from process data. For example, dissolution can be expressed as a function of other process parameters and material properties; such a model acts as a soft sensor for dissolution. An example can be found in the *ISPE PQLI® Guide: Part 2 – Illustrative Example*,[8] where dissolution is expressed as a function of drug substance particle size, magnesium stearate surface area, lubrication time and crushing force. These models are frequently data based and derived from multi-factorial DOEs.

*Real Time Release Testing*
Real Time Release Testing (RTRT) refers to the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.[1] In other words, RTRT refers to using the combination of material attributes and process controls as surrogates for an off-line method for end product testing. The surrogate may be an on-line (real time) analyzer, as for example NIR for residual solvents, NIR for content uniformity, or it may be a soft sensor where the quality is predicted from a number of other measurements. Empirical models are commonly used to calibrate real time analyzers or to derive models for soft sensors. Such calibration models should fulfil the requirements of any analytical QC method.

When the value predicted from a soft sensor model is to be used for release of the product, on-going process verification and maintenance of the predictive model could benefit from MSPC models. Such models are used to assure that the batches on which the model is applied were produced within the typical operating range for which the model was developed, to examine that the process behavior is similar to the time when the model was developed, and to assure that the assumptions prevailing when the model was developed are still valid. Variables to include in the MSPC models are generally identified from a risk assessment study.

*End Point Determination*

Modelling, in combination with real time analyzers or process data, can be used for "end point detection" or "end point control." For example, models to determine moisture percentages from NIR are empirical models based on multivariate analysis and are used to stop drying when a certain percent moisture is achieved.

Another type of an end point determination model is the Caterpillar algorithm, which works by assessing changes in the spectral data variation along time. It has been applied for real time end point detection for powder blends.[12]

Finally, through utilizing multivariate analysis and process data, empirical modelling can be used to monitor process signatures for end point determination problems.[11] This approach is a form of a soft sensor monitoring index of wellness of the process.

*Feed Forward Control*

The concept of adjusting the process conditions of a unit based on incoming measured disturbances through feed forward control is well known to the process systems engineering community and has been used for several decades. The methodology is also used in multistep/multi-unit processes where the process conditions of a unit are adjusted based on information of the intermediate quality achieved by the previous unit or based on raw material information. Both first principles and empirical models can be used for feed forward control. Given the measured deviation of the incoming material properties from the target value, the feed forward control adjusts the process conditions to achieve the desired output.

Kourti[9] presented a feed forward scheme utilizing multivariate projection space for a pharmaceutical product. That example illustrates a feed forward control scheme for Unit N based on input

information on the "state-of-the-intermediate product" from unit N-1. The settings for Unit N are calculated and adjusted such that the target value for Quality Y is met. A multivariate model was built to relate the product quality to the process parameters of unit N and to the "state-of-the-intermediate product" from Unit N-1. The "state of the intermediate product" is a multivariate projection of all the deviations of the raw materials and the process parameters up to unit N-1. From this model, a quantitative understanding was developed showing how process parameters in N and the "state-of-the-intermediate product" from N-1 interact to affect quality. This example is illustrated in Part 2 of this article, in the Examples of Models in QbD Framework section, example 2.

*Real Time Batch Process Control*

Real time control of product quality in a batch process can be attained using the simultaneous on-line adjustment of several manipulated variable trajectories such as temperature, material feed rates, etc. Traditional approaches, based on detailed theoretical models are typically based on non-linear differential geometric control or on-line optimization. Many of the schemes suggested in the literature require substantial model knowledge or are computationally intensive and therefore difficult to implement in practice. Empirical modelling offers the advantage of easy model building.

Empirical models utilizing latent variable methods have been applied to control product quality in batch processes. A multivariate empirical model predictive control strategy (Latent Variable Model Predictive Control (LV-MPC)) for trajectory tracking and disturbance rejection for batch processes based on dynamic Principal Component Analysis (PCA) models of the batch processes has been presented.[13] This model can be applied for drying, granulation, and other batch pharmaceutical processes.

***Setting Multivariate Specifications on Raw Material for Quality Control***

Duchesne and MacGregor[10] presented a methodology for establishing multivariate specification regions for incoming materials in order to maintain final product quality. Their idea was to control the incoming material variability for a fixed process. Empirical multivariate methods were used to extract information from historical data (where there was causal variability) and to relate the properties of the supplied raw materials and the process variables to the product quality. Additional data can be collected using DOE. The specification regions are multivariate in nature and are defined in the latent variable space. The incoming material is accepted if its properties fall within a multivariate target.

***Product Transfer (Scale-Up or Site Transfer)***

Scale-up and product transfer to a different site present similar problems in estimating the process operating conditions at a new plant to produce the same product that is currently produced in a different plant.

Both first principles and empirical models have been used in the past in scale-up; the type of model chosen often depends on the first principle understanding of the unit operation in question. A comprehensive example for design and scale-up based on first principles can be found for crystallization in McKeown, et al.[14] Similar examples can be found for other unit operations where first principles are well understood. In other cases, scale-up can be effectively based on empirical DOE based approaches.

An example of first principles model is thermodynamic modelling to predict the changes in temperature and relative humidity accompanying the phase change of a coating solution liquid to vapor. Such a model can allow the process engineer to substantially develop a coating operation design space using computer models prior to experimental confirmation batches. The approach is not only useful in early development, but also can guide scale-up. With a prudent choice of dimensionless parameters, a design space at the small scale can be translated directly to the large scale via this approach. A thermodynamic model for organic aqueous film coating is reported by am Ende and Berchielli,[15] and a working example is provided by am Ende, et al.[16] Phase diagrams can represent a compositional design space that drives to a specific desired phase/outcome; an example of this is crystal form/phase control during drug substance crystallization and drying.

Attempts also have been made to solve scale-up and site transfer problems with empirical models based on latent variables.[17] Historical data with process conditions and other information from both locations are utilized from previous product transfers to aid the transfer of a new product. These data may need to be enriched by a DOE for the current product. The two sites may differ in equipment, number of process variables, locations of sensors, and history of products produced.

***Continual Improvement***

During the lifecycle of the product, there are many opportunities for improvement in the manufacturing process as more knowledge is gained. Again, modelling can play an important role.

Process validation is defined as the collection and evaluation of data, from the process design stage through to commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.[18] Process validation involves a series of activities taking place over the lifecycle of the product and process. One of these activities is ongoing process verification, the goal of which is the ongoing assurance gained during routine production that the process remains in a state of control (the validated state) during commercial manufacture. In continued process verification, information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality product within commercial manufacturing conditions.

One way to demonstrate consistent production is to utilize MSPC, which can provide a monitoring scheme to check that: (1) the process is in a state of control, (2) there is no causal variability in the process, and (3) the observed variability is within the limits of common cause variation. The monitoring scheme usually covers process variables from several unit operations as well as properties of raw materials and quality (both final and

intermediate). For example, MSPC on all quality properties would detect if there is a drift in quality whereas MSPC on process parameters and attributes would detect a drift in the process and facilitate diagnosis as to the cause of the drift. When developing empirical models for process monitoring, it is important to consider all pertinent attributes and process measurements taking into account findings from the risk assessment.

MSPC models are empirical, based on historical data. MSPC charts may be constructed using measured variables directly (e.g., Multivariate Hotelling's $T^2$, multivariate exponentially weighted moving average) or using latent variable methods. In both cases, measured variables may be used as they are or transformed by utilizing previous knowledge (e.g., using meaningful transformations like logarithmic and inverse, using ratios of variables, or other calculated variables). A detailed discussion on these approaches can be found in article by Kourti.[19] When properly constructed, MSPC models can often detect abnormal events such as unusual variability caused by unknown disturbances and pending equipment failure. Two of the authors have presented examples from their respective companies in conferences, where unusual variability in auxiliary process parameters indicated impending equipment failure, such as from a kink on a flexible tube or partial plugged pipes.

It should be noted that MSPC is intended to detect variability that is causal; in other words, it is supposed to ensure that the process remains near the target operating condition. Therefore, when developing a multivariate model for MSPC, the model should be derived using batches manufactured only at the target process operating conditions and producing good product. To test the ability of MSPC models to detect unusual behavior, batches with known unusual behavior should be used as test sets.

It may seem counterintuitive to develop a model limited to a target operating condition, especially since development of a design space is intended to allow more flexible operation. It may be possible to create a common monitoring scheme that applies anywhere in the design space (not just the typical operating region); one of the ways to achieve this is by proper pre-processing of the data that enter the MSPC scheme.[19] Alternatively, the MSPC model can be redeveloped upon movement within design space to a new target condition.

In the product lifecycle, empirical models also may be used to analyze historical data for troubleshooting during investigations. Multivariate projection methods may be used that are extremely powerful for such purposes.[9] Much experience may be gained from historical process performance that can be utilized for process improvement. ◂

## Disclaimers

1. By E. Korakianiti: the views expressed in this article are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.
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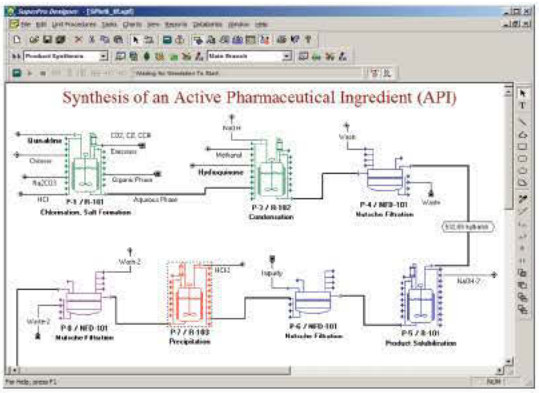


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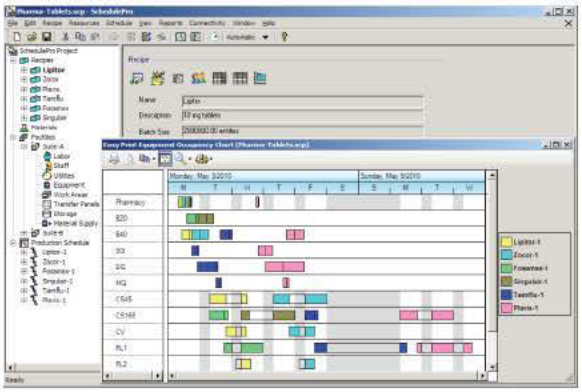

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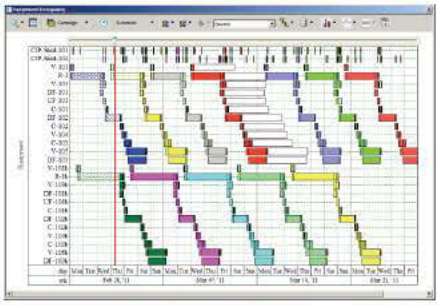

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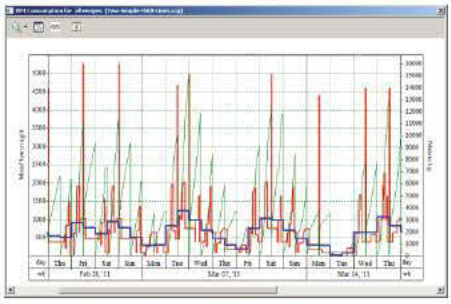

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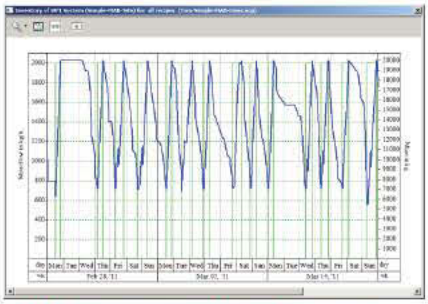

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# ISSUES WITH THE SAFE HANDLING OF ANTIBODY DRUG CONJUGATES

*Peter J. Marshall, CEng, Justin Mason-Home, John P. Farris, CIH, Erica L. Dahl, PhD, DABT and Fredrik Waern, PhD*

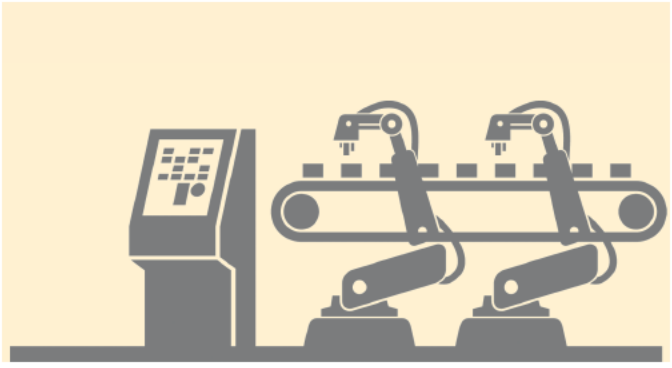
**This article reviews the significance related to high toxicity, and the complexity in determination of (bio) chemical exposure hazards and risks associated with ADC-related activities at all scales. High level approaches to mitigate and control these risks are proposed for consideration with the objective of establishing safe working environments and practices in a systematic, scientific manner, avoiding emotional or poorly informed responses which may, at the extremes, either create untenable risks of exposure or an overreaction to the extreme toxicity of the materials involved.**

**Antibody Drug Conjugates (ADCs) are one of the most exciting areas of drug development in biopharmaceuticals today.** The science of delivering therapeutic compounds in a potentially exquisitely targeted manner to disease locations within the body, while avoiding off-site toxicity, would appear to approach the ideal of Paul Ehrlich's "magic bullet" concept from the early 20th century.

The possibilities associated with ADCs have promoted the development of therapeutic agents which are amongst the most potent and toxic compounds encountered anywhere in the pharmaceutical industry. While potentially beneficial to the patient, these hazardous compounds increase the injury risk for those handling them in the industry environments, both in R&D and in manufacturing. The toxicity of the conjugates and individual component chemical entities present challenges not widely seen previously in biologics production.

This paper aims to review the background to ADCs, why they are an exciting prospect for the industry, and issues with establishing safe handling regimes in the workplace including engineering controls and supporting procedural requirements. It proposes a number of considerations to be made in deriving such an effective safe handling regime and potential multi-layered solutions.

ADCs bring together the disciplines of the chemist and the biologist, including biological processes carried out at near-ambient temperatures in finely controlled aqueous buffered media, as well as chemical synthesis processes involving high temperatures, non-aqueous solvents, exotic materials and forced conditions to create highly potent small molecules that have potentially significant side effects at very low doses. It is a challenge to bring these two disciplines together to deliver ADCs in a safe and effective manner.



It is the aim of the authors to allow those involved in ADC-related activities to develop an understanding of the (bio)chemical exposure hazards and risks associated with their activities, with the objective of establishing safe working environments and practices in a systematic, scientific manner, avoiding emotional or poorly informed responses which may either create overreactions or unacceptable exposure risks.

## Background to ADCs

ADCs are pharmacologically active conjugate substances generally made up of three major components, which individually or in combination may be highly hazardous substances:

a. An antibody or antibody fragment designed to selectively and specifically bind to an identified disease target (usually a cancer cell receptor).

b. A linker—a chemical link between the antibody and payload molecule designed to connect the payload to the antibody and then release it at a suitable location (often inside a cancer cell).

c. The payload—a pharmaceutically potent and toxic active molecule bound to the antibody by the linker molecule, designed to kill the target cell.

The antibody or antibody fragment has two functions: firstly it enables highly specific delivery of the payload component to an identified disease target binding site. The antibody also reduces the risk of undesired effects by keeping the highly potent payload molecule in a shielded or less toxic form until bound to the target site, where the ADC will be processed by the target cell, releasing the drug substance.

The specificity of delivery allows the payload to be present in a relatively small overall dose (in comparison to traditional chemo-therapy agents) further reducing the risk of toxic off-target effects in the body. Some of the payloads currently under consideration for use in ADCs were initially rejected for pharmaceutical use in the unconjugated or pure form due to unacceptable toxicity.

Binding a protein to a small molecule drug to reduce toxicity is an established strategy in pharmaceuticals. For example, the drug product Abraxane (from Celgene Inc.) uses albumin to improve

the stability and reduce side effects from the active paclitaxel component. ADCs differ through the use of the antibody or antibody fragment, which also provides targeting to a specific site.

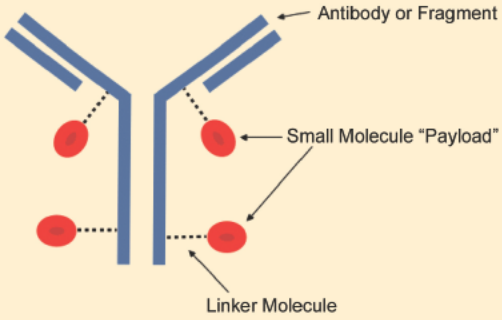
The recently approved ADCs Adcetris (from Seattle Genetics, Takeda, Millenium, treating Hodgkin's lymphoma) and Kadcyla (from Genentech, treating HER2-positive breast cancer) are showing effectiveness. Large numbers of candidate drugs are currently in development,[1] and surveys suggest that ADCs will form one of the largest areas of future development in the industry, particularly in the field of oncology.[2,3]

Antibody-based targeting allows researchers to consider many targets which may previously have been difficult to reach safely with effective pharmaceutical payloads. As a result, there is a rapidly developing research base in all elements of ADC application (targets, antibodies, linkers and payloads). Researchers aim to identify antibodies specific to target antigens, linkers which are able to maintain extended plasma stability with the ability to release the payload in very specific intracellular target locations while avoiding reductions in antibody binding efficiencies, and payloads of ever-increasing potency, ensuring effective action even where antigen binding site frequency is low.

Most investigation has been directed towards oncological and haematological indications, using payloads of increasing potency. In addition, there are developments in the neurological field, specifically for Alzheimer's disease, using payloads with potent anti-oxidant and anti-fibrillogenic properties. In a number of cases, ADCs have been designated orphan drugs in order to promote their development,[12,13] due to their potential to treat previously intractable conditions.

For the payload, most oncology ADCs in development make use either of auristatins from Seattle Genetics or maytansines from ImmunoGen, both of which are anti-microtubule agents. Other classes such as DNA alkylating agents (including pyrrolobenzodiazepine (PBDs), cyclopropabenzidole (CBI), indolinobenzodiazepines (IBDs), and duocarmycin) and DNA double-strand breakers (calicheamicin, esperamycin) are also emerging, providing a range of payload options for the conjugate drug developer.

**Figure 1** Components of a typical ADC molecule




All these small molecules exhibit genotoxic activity and very high potency and toxicity. For comparison, the PBDs exhibit Daily Equivalent Dose (DED) values of around 13 µg/day,19 compared to an example highly potent aromatase inhibitor (anastrozole) with an equivalent DED of 1 mg/day (MHRA PAR UK/H/911/001/DC). A further concern is that the toxic effects of exposure to such molecules are generally severe and irreversible, unlike some other highly potent drug effects (such as those demonstrated with peptide hormones), where the effects of exposure may be less severe or reversible.

In the past, some products have used radioisotopes as payloads (such as Zevalin, marketed by Spectrum Pharmaceuticals), but these are relatively uncommon in development and the safety considerations of handling radioisotopes will be covered by national radiological standards and guidelines which fall outside the scope of this paper.

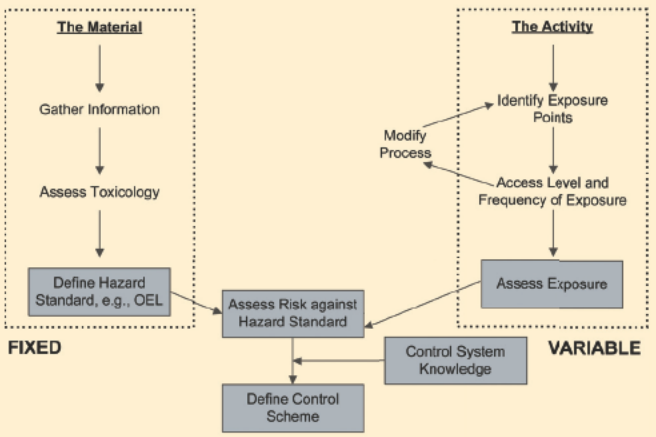
While there is great interest in the scientific literature as to the undoubted potential provided by ADCs for therapeutic benefit, there is little discussion of the issues around the safe handling of such highly toxic compounds in the laboratory and manufacturing environment. Examples of the impact of occupational exposure to highly toxic pharmaceutical materials are not widely reported, and so awareness outside specialist toxicology and occupational hygiene circles is limited. However, cases that have appeared in the literature provide useful and salutary background to the impact of undesired exposure.[4] The standard approaches used in risk assessment for chemical exposure control will apply, but with additional considerations reflecting the extreme toxicity of the materials being handled.

Considering the generic exposure control approach, the risk of injury from exposure to chemicals during their manufacture and handling is a function of:

1. the occupational toxicity (hazard) of the material; a fixed function of the material,
2. the exposure potential (risk); a variable depending on a number of factors related to the process, the equipment used, and the procedures applied in the handling activity.

While the conjugated ADC may be considered to be of relatively low toxicity and reduced bioavailability in an occupational setting compared to traditional "potent" small molecules, there is scope for exposure to the individual elements during their manufacture, as well as during the subsequent conjugation and purification operations. These molecules potentially present a significantly greater toxic hazard. The generic process to defining a robust and appropriate control regime is summarized in Figure 2.

Figure 2 Exposure control scheme definition process




When setting appropriate safe working levels, all potential exposure routes should be considered including:

- Inhalation, either as direct transfer in the lung, or by ingestion via the cough-swallow response
- Subcutaneous transfer, either through open wounds or compromised skin barrier, or direct transmission (e.g. needle stick).
- Transdermal transfer, with a molecule typically carried by organic solvent in small molecule manufacture
- Ocular, by contact of the eyes with contaminated hands or gloves; or airborne deposition.
- Ingestion, typically by mechanical transfer from contaminated hands (generally a relatively insignificant route of exposure in most well controlled facilities).

It is important to consider all the above as bioavailabilities may vary depending on the route. As such, it is important to maintain a view across all materials, and not to concentrate on the highly potent and toxic payload alone at the expense of all others.

One point to note when considering the toxicity of the ADC and individual components is the relative size of the component molecules. While the payload and linker may have molar masses in the several hundreds of daltons, the antibody will typically have a molar mass of around 150,000 daltons, though antibody fragments may be significantly smaller. As such, the payload element of the ADC may only constitute less than 0.5% by weight of the total; a potentially important fact when safe exposure levels are typically quoted in mass terms. Of course, with smaller antibody fragment utilization this effect will be reduced and the toxic payload will constitute a greater proportion of the compound mass.

Following identification of acceptable exposure levels in each case, the consideration of the risk of exposure in each handling activity may be considered, and the requirement for additional controls identified in line with standard current exposure control design and specification.

## Toxicology of ADCs and Components

As stated previously, toxicity is a fundamental property of a material and is not altered by factors such as quantity or physical form (e.g. as solid, blend, solution etc.). For each activity, the Occupational Exposure Limit (OEL) or other related limit value to establish acceptable workplace exposure levels will be defined by the materials present, whether they are pure payloads or other components, conjugated drug product, or mixed intermediates with or without residual traces of free components. The calculation of an acceptable OEL for each ADC component in each case must be defined by suitably qualified and experienced toxicologists.

The process of developing an OEL for a substance typically includes a number of steps such as selecting a dose descriptor (e.g., NO(A)EL/LO(A)EL, BMD10, EC50) from relevant studies, and choosing a mode of action in order to decide if there is a threshold or non-threshold effect. If the critical effect is not likely to have any relevant toxicological effect below a certain exposure (i.e., threshold) then a set of assessment factors, also commonly called uncertainty factors, is normally applied on the most relevant dose (e.g., LO(A)EL or NO(A)EL) used in the critical study. The uncertainty factors typically takes into account for intraspecies differences, interspecies differences, differences in duration of exposures, dose-response and toxicokinetics issues, and the amount and quality of data available.

An OEL for known or suspected direct-acting mutagenic carcinogens (e.g., payloads) for which no threshold is expected is often derived in a different way since any exposure is assumed to increase lifetime risk. For these type of compounds the dose (or concentration) expected to induce an increased lifetime risk for cancer of $10^{-5}$ or $10^{-6}$ is estimated by statistical extrapolation from the experimental data (IPCS, ECHA).[14,15]

While the toxicities of the individual components may be reasonably well understood, it is important to realize that the manufacturing process will create a number of intermediate compounds as well as the final product, which may present a range of unexpected toxicities and exposure challenges. Furthermore, research synthetic chemists will be synthesizing intermediates, analogues and other small molecules as part of basic research, which may have greater or lesser toxicity compared to the final product molecule.

Finally, recent changes to European GMPs have proposed a toxicology-based Permissible Daily Exposure (PDE) as the basis for cross-contamination assessment and mitigation evaluation.[16] While this is outside the scope of this paper, it should be noted that the presence of ADCs and, potentially, excess residues of more toxic components will result in low PDE values. These low values may potentially mean enhanced facility segregation and equipment dedication is required.

### Payload

The most potent and highest toxicity component is the "payload" element. These include such molecules as auristatins, maytansinoids and PBDs as noted above, as well as other emerging classes noted previously.

The toxicities of such molecules vary, but in many cases they are some of the most toxic materials handled in the industry, with OELs recorded by the authors ranging from hundreds down to single figure nanograms per cubic meter of air (200 to 1 ng/m$^3$), expressed as 8-hour time weighted averages. These low OELs correspond to exposures that are lower than some "generic" limits for genotoxic compounds.

For example, for drug impurities with limited data for which there is some evidence of mutagenicity (such as a structural alert), an acceptable daily exposure of 1.5 µg/day has been established, based on a Threshold of Toxicological Concern (TTC) approach, and corresponding to a theoretical 1 in 100,000 excess lifetime risk of cancer.[5] Applying the commonly used assumption that a worker breathes 10 m$^3$ of air per 8-hour shift, this daily exposure limit would correspond to an OEL of 150 ng/m$^3$.

There is a continuing drive to create ever more potent payloads to improve the efficacy of the ADC treatment in cases where antigen binding site numbers or efficiencies may be low. As such, it is likely that, in the future, there may be an increasing requirement to be able to safely handle ever more toxic pure payload substances, with OELs in the single nanogram per cubic meter level. While experience in handling materials of similar (or greater) potency, for example peptide hormones and prostaglandins, has existed in the industry for a number of years, this capability is extremely specialized and limited to organizations experienced in handling such materials and specialist consultancies. Furthermore, the toxic effects of the materials being considered by this paper are generally more severe (e.g., genotoxicity) than those seen with, for example some hormone products, and may be less reversible.

### Linker

The linker must be stable enough under physiological conditions to allow the payload to be delivered to its target, but readily cleavable under the correct conditions.[7] Cleavable linkers include hydrazones, which are unstable at the low pH of the lysosome; hindered disulfides, which are cleaved in the cytosol by specialized enzymes; or peptide linkers, which are cleaved by lysosomal proteases. Non-cleavable linkers (i.e., thioethers) release the payload only after the antibody has been degraded in the lysosome. An alternate strategy is an engineered antibody which may make use of thiol conjugates at specific sulphur-containing amino acids, or unnatural amino acids that may be conjugated to the payload by cyclotransferases or transglutaminases.[8,9] Flexible polymer linkers, which may allow greater drug loading per antibody, are also being investigated.[7]

Linking strategies that take advantage of the properties of endogenous amino acids (such as engineered antibodies or peptides) are unlikely to be toxic on their own, or to significantly contribute to the toxicity of either the antibody or the payload. The toxicity of other types of linkers would need to be evaluated in a case-by-case basis. Potential issues include the possibility of linking to endogenous proteins or other cellular macromolecules, or altered immune responses.[10] In preclinical studies of Kadcyla (ado-trastuzumab emtansine), the thioether linker used in the construction of the ADC did not contribute significantly to toxicity.[11]

### Antibody

The relatively low toxicity of antibody proteins, and the common processing of such macromolecular materials in enclosed solution or suspension forms, has allowed the risk of intolerable exposure by main traditional routes (inhalation, ingestion and skin absorption) to be considered to be relatively low. In addition, the effectiveness of uptake of such large biologically derived macromolecules by traditional exposure routes (airborne inhalation and ingestion) may not be particularly effective compared to comparable small molecule exposures, due to instability of proteins in the gastrointestinal tract as well as differences in deposition along the respiratory tract.

The variability of uptake of proteins by inhalation is reviewed by Pfister et al.[6] They suggest that the inhalation bioavailabilities of large antibodies such as IgG may be significantly less than 5% of the exposure dose, though that of other antibodies and fragments may be significantly higher. Conversely, exposure by inhalation, dermal contact and subcutaneous transfer can lead to an allergic response including inflammation, rash formation or asthma. This is a common warning for pure protein products.

### Conjugates (Antibody-Linker, Linker-Payload, Full ADC)

In general, once the antibody is conjugated with the other elements in a purified stable form, there is only limited availability of the payload and linker to cause toxic effects, unless the ADC is exposed to chemical or physical challenge.

An area of concern is the presence of unconjugated components as impurities in the final conjugate. In practice, as noted previously, the relative mass of such impurities may be small compared to the total mass of conjugates, and as a result, the weight of hazardous materials will be relatively small even if derived from degradation of the ADC. This may be relevant where there is potential for release of payload in undesirable locations, such as through acid hydrolysis of linker binding in gastric exposures, or through exposure to oxidizing cleaning agents in manufacture.

The creation of partial conjugates, specifically the formation of payload-linker compounds without the antibody, avoiding the manufacture of pure payload, will not completely remove the toxic exposure risks associated with the latter, as the linker can be cleaved metabolically and the free drug or payload is released to exert effects in the body.

### Exposure Assessment in ADC Synthesis

The assessment of emissions into the working environment and potential worker exposures starts with a complete and thorough definition of the activities to be carried out where there is a demonstrated likelihood of a hazardous material being present. This includes all normal synthetic chemistry and pharmaceutical processing steps (sampling, weighing, dispensing, charging), cleaning, sampling and analysis, maintenance of potentially contaminated systems, and recovery from potential system failures.

Given the known toxicities of payload materials, activities such as payload manufacture and handling of pure payload material prior to conjugation, and especially any processes involving open handling of such materials, especially in a dry powder form, should be treated as presenting a high risk of unacceptable exposure. Similarly, ancillary activities such as Quality Control (QC) testing and cleaning, where exposure to the payload either as a trace residue or component of a sample may occur, should also be considered.

The assessment needs to consider:

- The material to be emitted and its physical form
- The potential scale of emission
- The likelihood of emission in each case
- The likelihood that the emission and subsequent exposure might be detected.
- The relative position to the emission of the potentially exposed worker(s).
- The severity of the effect of exposure
- The presence of any empirical occupational hygiene monitoring data that scientifically demonstrates workplace levels
- The extreme levels of uncertainty involved when handling and measuring highly potent and toxic APIs.

In the small molecule field, it is usual to initially consider reliance on experience and data from similar previous applications. This can be problematic with ADC payloads and other extremely hazardous chemicals, as such data is typically either extremely limited due to the rarity of handling such hazardous materials, or is based on extrapolated data from less toxic material assessments which may not have used suitably sensitive methods to provide data relevant to determining the required “safe” working levels appropriate to ADCs.

Other commonly used methodologies for determining the sources and risk of emissions include a number of tools such as HAZOP, FMEA and so forth to supplement experience from similar situations elsewhere. As will be discussed later, the extreme toxicity of the materials involved creates a degree of uncertainty in assessments, and methods such as these may be difficult to calibrate to the levels of exposure of concern, either to reflect the uncertainty or the impact of relatively small emissions that might otherwise be considered acceptable by the unwary with limited or no experience with assessing the risks associated with molecule of such high toxicity. If such approaches are to be used, it is essential that a team suitably experienced with handling materials of such extreme toxicity carries out the activity, to ensure that all areas of significant risk are appropriately identified and evaluated.

The particularly challenging aspects of exposure control problems created by the manufacture of ADCs at all scales are generally related to the specific issues created by the very high toxicity of the payload and conjugates containing the payload. The toxicity and safe handling approaches related to the pure small molecule linker and large molecule antibody are either relatively well-understood or present different challenges, for example sensitization via antibody exposure, and will not be considered in detail in this paper.

The processes used for the manufacture of payload and subsequent conjugations are typical “wet chemistry” and associated purification and isolation steps including chemical reaction, chromatography distillation, filtration, crystallization, drying and lyophilization, with solvent recovery and emission controls.

Typically the scale of operation for ADC development and manufacture including individual component compounds can be relatively small compared to “normal” potent API manufacture, due to the high potency of the materials and therefore the small quantities required. While this may avoid some of the issues of major spillage recovery associated with larger scale potent API manufacture and subsequent formulation, it must be remembered that the payload materials may be several hundreds of times more toxic and hence even relatively small emissions present significant risk.

Major concerns during synthesis and conjugation will include all activities where manual intervention is required, transfer of materials between processes except in sealed transit routes, and in recovery and storage of the high toxicity material in a form which may present enhanced emission risks by certain routes; for example as a dry friable solid for airborne transfer, or as a solution in an organic solvent for transdermal transfer.

The high toxicity of the payload and potential toxicity of the ADC requires a more rigorous consideration of the routes of exposure than might be typical for small molecule applications where typically only airborne and (occasionally) surface transfer routes are considered. The extreme toxicity of the payload warrants consideration of all routes, with control of hand contamination in particular being a concern as this is a major transfer route into ocular and ingestion routes of exposure.

The high toxicity and uncertainty of exposure uptake efficiencies means that other activities that may lead to exposure to trace levels of residues, such a might occur during manual cleaning of contaminated equipment may be significant, and the potential and mechanisms for equipment and containers to become contaminated on exposed external surfaces should also be assessed.

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Waste streams from chromatography may contain trace amounts of impurities, unconjugated and partially conjugated components and care should be taken in understanding the composition and potential exposure profile.

Cleaning of ADC facilities will generally apply standard protein residue cleaning for the antibody with dissolution of the residues. While the risk of exposure is likely to be small, care should be taken in selection of cleaning methods to avoid the risk of de-conjugation leading to release of the pure payload, which may not be degraded by such agents and may present exposure risks in effluent streams.

The use of decontaminating agents, for example strong oxidizing agents under near ambient conditions, commonly used in biologics cleaning activities may not be effective in degrading payload molecules. The mechanism of action for the specific cleaning agents to be used should be carefully assessed to determine whether there is a realistic probability of releasing payload in a toxic form as a result of cleaning processes.

The review of major exposure mechanisms should include not just process equipment but also ancillary areas, for example extract filters, ductwork, lab coat laundry, and equipment cleaning areas.

## Exposure Control

Exposure control system design relies on a risk assessment based around a comparison of the exposure potential to a defined acceptable limit, and the use of additional controls to mitigate or reduce the former as required. This relies on an understanding of the acceptable standard, the exposure risk and scale in the particular case being considered, and the capability and effectiveness of individual or combination control approaches.

Ideally, considering an airborne exposure route, it is desirable to directly compare a measured airborne concentration to a scientifically defensible OEL as suggested in Figure 2. OELs have been set for some of the main payload molecules as well as for some of the ADCs, and validated air and surface monitoring and analytical methods have been developed for some of these.

However, industrial hygiene studies on these materials are currently limited. Where such data are not available, for small "potent" molecule manufacture a form of qualitative assessment has sometimes been applied, using risk based exposure models. These may be either internal company systems or more widely available tools such as REACH ART or the German EMKG tool, all of which are based on experience and historical exposure data.

The problem with the use of such models is that they are not designed or calibrated for achieving the acceptable levels for highly toxic materials with OELs at the levels proposed for ADC payloads. These tools should not be relied on to provide a robust exposure control solutions due to the extreme toxicity of the payload material. In practice, additional controls are required because the airborne and other exposures for these materials are uncertain.

1. A pharmacologically active ingredient or intermediate with biological activity of approximately 15 µg/kilogram of body weight or below in humans (a therapeutic dose at or below 1 mg).
2. An API or intermediate with an OEL at or below 10 mg/m$^3$ in air as an 8-hour time weighted average (TWA).
3. A pharmacologically active ingredient or intermediate with either high selectivity (i.e. an ability to bind to specific receptors or inhibit specific enzymes), or with the potential to cause cancer, mutations, developmental effects, or reproductive toxicity at low doses, or both.
4. A novel compound of unknown potency and toxicity.

The most concerning exposure route is likely to be inhalation: Direct skin exposure can generally be controlled through appropriate gowning and PPE (gloves), excellent laboratory practice, and good training, while ingestion exposure can be minimized by practicing effective hand washing and similar hygiene procedures. Robust safety procedures can prevent secondary contact that can occur during removal of contaminated clothing.

The role of potent compound safety awareness and training cannot be over-emphasized as compliance with procedures is critical to effective exposure control, particularly at the levels associated with ADC operations. All staff who may potentially come into contact with the materials must receive rigorous training, including management, maintenance and cleaning staff, not just operators and researchers.

The ADC itself is not likely to penetrate intact skin given its large size. There will be a dermal component to the small molecule handling but this can again be controlled by engineering controls at the point of potential emission, proper use of PPE, and robust procedures. Cleaning equipment with organic solvents is a process where dermal exposure is a potentially significant risk.

Where potentially contaminated materials are removed from controlled areas without effective surface decontamination, there is the issue of uncontrolled "tracking" or mechanical transfer of materials outside the controlled environment by direct contact on hands. Drug substance or drug product may migrate outside the processing suite if the facility cleaning and decontamination procedures are not followed correctly and diligently.

As will be discussed later, contamination will never be visible or readily detectable and therefore it is critical that the workforce are aware of these risks and are familiar with the mechanism by which material may migrate, typically by airborne or mechanical transfer on surfaces as noted above, and how uncertainty in detection will be managed.

## Identification of Appropriate and Effective Controls

Once exposure potentials are understood and their acceptability has been assessed, any requirements for additional controls should be considered. Key reasons for applying additional controls include:

- To reduce exposure to a level where it is assessed not to exceed a nominal acceptable level. This may be a single system (e.g. glovebox or containment isolator), or a combination of systems where a single system may not be sufficient or has significant performance variability.
- To provide additional protection against failure or reductions in the effectiveness of the primary control system(s) above. This is especially important where a failure may not be immediately detectable.
- To provide reassurance that the zone of significant exposure risk may be controlled, typically this includes ventilation system design, personal decontamination and other systems designed to prevent the spread of material to areas where exposure could is not anticipated.

A critical feature of exposure control system design is that options for effective control are case-dependent, and applying a single approach to all potential exposure risks based on the toxicity of the material alone is likely to result in either ineffective or excessively restrictive controls in many cases—a "toxicity x = engineering solution y" approach should be avoided.

It can be appropriate to use some general strategies—for example using redundancy to mitigate uncertainty, and using similar exposure control approaches for and processes with similar exposure risks—but care must be taken to ensure that other factors which may differ, for example: GMP and ergonomic requirements, are considered in the controls definition.

The traditional approaches to control are based on the well-established Hierarchy of Control:

While elimination is often considered impossible in pharmaceutical applications where "the molecule is the product", this is not strictly correct for payloads. For example, it may be possible to generate a molecule comprising the incomplete payload attached to the linker prior to completing the formation of the payload, thus avoiding creating isolated pure payload and avoiding the risks associated with isolating the most toxic form of the molecule. Drug developers should be encouraged to consider this approach, as it minimizes the risk to staff and reduces reliance on expensive engineering hardware and user compliance with procedures.

Substitution is also often overlooked. In this case, it can involve the avoidance of hazardous forms of the materials—maintaining materials in aqueous solutions rather than isolating dry solids or using organic solvents that might increase potential for dermal transfer, and telescoping chemical synthesis steps to avoid isolation. Again, such process philosophies should be promoted in synthesis and conjugation development processes.

The application of highly engineered containment systems is relatively common in potent small molecule handling activities. Conversely, biopharmaceutical operations have typically required lower levels of containment due to the relative rarity of such toxic materials in their activities, and by greater GMP-related concern to prevent product contamination. As a result, where containment systems have been provided in biologics processing, they have generally been installed for the purposes of sterility and aseptic operation.

There is wide experience in the pharmaceutical industry in the specification, effectiveness and operation of engineered exposure control systems, including well-developed test and performance verification methods. Equipment selection is generally based on experience with similar applications, both quantitative and qualitative, but the available performance data may be limited to cases from less highly toxic applications. As a result, the limits of system containment capability and resilience to variations in operating methods may not be well understood.

As stated previously, ADC payloads are in the group of the most highly potent and toxic materials encountered in the pharmaceutical industry, which would indicate a need to use the highest containment approaches available. Further to this, in the future, the use of remote or automated operations, or both, may be considered for applications involving these materials, in order to further separate the worker from the source of exposure.

The use of administrative controls, including well-defined procedures and techniques, highly developed training with worker validation, biological monitoring and optimized workplace location, and the use of personal protective equipment (PPE) will not provide a suitably robust control when used on their own, because of the extreme potential challenges ADC payloads may present. Therefore these controls should only be considered to support engineered containment and higher levels of control. In particular, PPE and associated respiratory protective equipment (RPE) should be used as an additional and redundant control.

### Demonstration of Effective Performance

Following selection and installation of control systems, verification of effectiveness is required, particularly in the performance of engineered control systems. This is essential as the selection methods, usually based on similar but never identical applications, may not be valid and assurance is required before putting a system into full operation.

It must be noted that some of the traditional tools for managing hazardous substances encountered elsewhere in industrial activity are not available for highly toxic compound management. Such classes of hazardous substances as reactive gases, volatile organic compounds and ionizing radiation emitters can be monitored very effectively in real-time using continuous monitoring devices or direct reading instruments, or both. These results can be immediately compared with either government sanctioned or company-set limit values, allowing immediate action to be taken in cases where exposure standards are exceeded.

While some real-time analytical methods using particle counts and physical tests such as helium or ammonia leak testing have

been applied specifically to isolator performance testing and fault detection, these are not specific to the material of concern and are generally not suitably sensitive to identify whether a significant overexposure risk exists in normal operations, except in cases of major equipment failure.

The lack of such specific continuous or real-time monitoring technology for highly toxic compounds means that effective quantitative assessment is restricted to discrete sample collection through industrial hygiene pump and filter monitoring methods followed by remote chemical analysis of samples.[17] Due to the complexity of these processes, the cost of monitoring is substantially higher than that incurred for regular hazardous substances, which in practice can lead to small data sets and high uncertainty. Further to this, the requirement for remote sample recovery and chemical analysis in a laboratory environment means that sample results are not immediately available, and delays in receiving and resulting analysis data may be significant. As a result, the turnaround in results and subsequent interpretation may take several days, preventing rapid identification and response to excessive exposure levels.

Prior to introducing toxic materials, it is common to test the containment performance of systems using a low-toxicity surrogate. This quantitative testing is carried out first with discrete air and surface sampling, allowing a level of assurance to be obtained in the exposure control capability of the installed systems and procedures, prior to introduction and assessment with the actual material of interest.

Following this, the optimum test of effective performance is to measure the quantities of the material of concern at appropriate points in the transmission path (for example; airborne sampling in the workers' breathing zone) and to compare these data to the required acceptable levels using appropriate statistical analysis as necessary.

Where very low acceptable exposure limits exist, it may be difficult to do effective analysis. Analytical methods typically require picogram (millionths of a milligram) levels of sensitivity to recover measurable amounts of material from sampling media exposed to concentrations at or near the OELs found for ADC payloads. Industrial hygienists will require this capability in order to detect and quantify exposures at the levels required to meet the extreme OELs. However, validated analytical methods with the required sensitivity have been developed in the past by specialist analytical laboratories for certain surrogates and by the authors for both ADCs and the individual payload classes.

Both the sampling activity and statistical analysis of the limited datasets typical of potent-compound monitoring exercises and the assessment of compliance to an acceptable limit are time-consuming and highly complex activities, and should only be carried out by individuals with specialist industrial hygiene expertise in the field. The analysis itself is also typically complex, time-consuming and requires highly competent analytical staff.

## ADCs and Control Issues

As noted previously, the safe handling of materials of very high toxicity—for example peptide hormone products—has been achieved for a number of years in the industry, albeit the number of companies handling such materials and achieving such levels of robust exposure control is small, and expertise in this area is therefore limited. Depending on the exposure profiles that occur in the development and manufacture of ADCs, the level of control required may be anticipated to be at least as high as current highly potent small molecule drugs. There are a number of key factors pertinent to the handling and processing of ADCs in development and manufacturing scale.

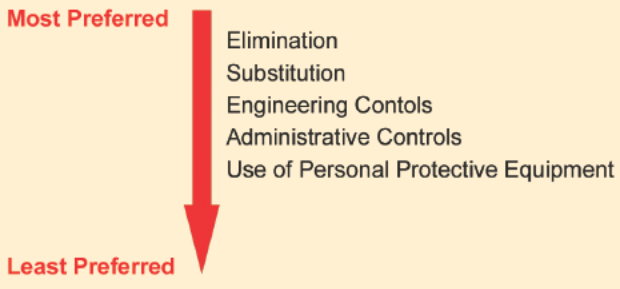
## Uncertainty

Uncertainty in the assessment and control of materials of such high toxicity as ADCs and specifically the highly potent and toxic payload is created by:

1. The impact of even relatively small exposures and the fact that amounts measured in billionths of a gram may present significant risk.
2. The difficulty in robustly measuring to a high level of statistical confidence with the sensitivity and precision required to demonstrate exposure to acceptable levels without incurring excessive costs and delay through extended sampling and analysis programs.
3. The lack of knowledge of the capability and robustness of standard containment systems such as isolators or ventilated enclosures (including laboratory fume hoods) to routinely achieve exposure control to the acceptable levels required for materials of such toxicity for all operations.
4. The inability to detect failures rapidly except where exposures may be at thousands of times the acceptable limit.

The inability to obtain high confidence in some of the quantifiable elements of the standard exposure control design approach leads to an increased degree of uncertainty compared to similar activities with less potent materials, and has potentially significant impact on resulting risk assessments and control strategies.

Figure 3 Hierarchy of control



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Even where relatively small quantities of material might be handled, this potentially creates the potential for significant levels of exposure. For example, assuming the 0.15 µg TTC value for a payload, 1 gram is equivalent to the TTC of 6.7 million people on the basis of one day's exposure. While it may not be possible to carry out a physical mass balance of processes handling such materials, great care is needed to develop as complete as possible an understanding of where material may be or could transfer to, and how well controlled it is.

In addition to this must be considered the toxicology of the linker, the antibody and combinations of these. Linker molecules are anticipated to be relatively lower in toxicity, but no data are currently available to show this. In practice, such reactive molecules may also be mutagenic. Antibodies are generally likely to be unavailable by inhalation or ingestion as discussed previously but one cannot rule out a sensitization potential as it is known that treatment with antibodies can cause hypersensitivity reactions.[20]

Unlike assessments related to less toxic material handling in the small molecule arena, widely used qualitative methods are not always valid as noted previously. For such challenging materials, it is essential to apply a coherent scientific approach based on the assessment and analysis of robust quantitative data with an understanding of the uncertainties involved in their generation, and then to compare with appropriate quantified tolerable limits, for example OELs.

The quantified evaluation of exposure routes, and hence the ensuing levels of exposure, is challenging for molecules of such toxicity. Traditional airborne sampling and chemical analysis methods may provide levels of sensitivity suitable only for extended rather than task-based analyses, and finding suitable surrogate alternatives with appropriately sensitive analysis methods to achieve the latter may be problematic.

For example, consider an analysis capable of quantitatively detecting 50 picogram ($50 \times 10^{-12}$ gram) of material on an airborne sample filter. Such analytical sensitivity is the reported limit of quantification (LOQ) for a generally available surrogate (naproxen sodium) at this time.

For a 30-minute sample using a standard IOM sampling pump (which samples air at 2 liters per minute), the limit of detection (LOQ) will be:

$LOQ = 50 \times 10^{-12}/2 \times 10^{-3} \times 30 = 8.3 \times 10^{-10}$ g/m$^3$ ( = 0.83 ng/m$^3$)

Higher volumetric rates are validated for other sample systems such as the 37 mm cassette, which will reduce the LOQ by a commensurate amount.

Where the sampling LOQ is a significant fraction of the OEL (> 10%), the assessment of quantified data becomes problematic unless large datasets are generated to mitigate statistical analysis concerns. Increased sensitivity can only be achieved through increasing the volume of air sampled, either through use of alternative validated sampling systems, or through extending the sampling time. The latter may not be desirable if the aim of the monitoring activity is to assess the exposure associated with a specific task, rather than the aggregate exposure over a number of tasks of shorter duration than the sampling period.

It is essential that highly competent hygiene specialists are involved in the collection and assessment of data, including the application of suitable statistical analysis[18] to ensure coherent assessment of what the data is demonstrating, and to ensure effective actions are taken after the results are seen. The variation in the data that sampling may generate is not well-understood without specialist competence and simplistic assessments that may be appropriate in less challenging applications are not valid with analysis methodologies so close to the limits of current capability. Similar calculation limits apply to surface wipe sampling methods. For non-airborne exposure routes, the assessment of exposure will be typically based on data derived from such surface sampling and assumptions as to the effectiveness of subsequent transfer; the latter may require a degree of conservatism in the absence of supporting data to the contrary.

Hence the sampling data used to justify system performance may have a high degree of uncertainty. Further to this are issues with effective preservation and analysis of the sample due to the extremely small quantities involved.

The selection of appropriate engineered control systems is based on historic experience and knowledge of the strengths and weaknesses of each option, or combination thereof. Unfortunately, most historic data has been generated to justify selection when less toxic materials are being handled, relative to what is being considered here. As such, there are little data available outside the companies already handling materials of such toxicity to safely justify assumptions on the performance of particular systems in specific applications.

Furthermore containment equipment vendor claims of containment performance may be based on very limited data obtained under conditions that would not be encountered in the workplace. While this data should not be discounted, it may not support the definition of a robust containment performance envelope presenting effective performance under a range of conditions and may not be "task-based".

Similarly, there is little data on the propensity of systems to routinely or occasionally fail to contain to the levels required for ADC payloads rather than for small molecule applications with OELs a factor of a thousand times greater. As such, a system might be demonstrated to be effective on initial installation, but without routine repeat sampling, may unknowingly present intolerable exposure risks on a regular basis. Most engineered containment systems are highly susceptible to performance variation even when there is robust compliance with operating procedures. With highly toxic materials handling, such variations may lead to routine undetected overexposure. As a result, systems which limit the

users capability to vary the method of operation, or which are resilient to such variations, such as containment isolator systems which are most likely to provide routinely effective control are preferred. Further to this, automated systems that limit operator exposure through remote or "through the wall" location might be considered in future, as materials may present even higher levels of toxicity.

The difficulty in detecting exposures rapidly through human senses and other physical methods such as particle counting is similar to that seen in highly potent small molecule APIs, exacerbated by the potentially extreme toxicity of the payload molecules. With ADC payloads having potential OELs in the low nanogram per cubic meter level, there is little chance of identifying failures, as safe exposure levels are many orders of magnitude lower than typical reported visibility limits (~50 to 100 mg/m$^3$ under strong light ("Tyndall Beam") illumination in air and ~ 4 mg per 100 cm$^2$ on surfaces).

## Culture

While materials of similar toxicity are successfully handled and produced safely on a daily basis—for example sex hormones and peptide hormones—the specialist knowledge and techniques to achieve this have typically been limited to the small number of companies operating in this field. These companies have often suffered serious health effects in their workforces in the past and have developed the necessary expertise in the safe handling of these materials from these experiences.

The development of ADCs is typically carried out within the biopharmaceutical side of the industry, and as such may be considered to be a "biological" process, though it includes traditional small molecule processes including toxicant synthesis and modification. The issues associated with handling these materials perhaps have more in common with issues in small molecule manfacturing, for example exposures associated with "wet" chemistry and the application of engineered containment systems.

As well as in large multinational organizations, ADC development is also being driven to a large degree by smaller research-based companies with leading-edge expertise in the individual elements of ADC molecule assembly, but with a level of toxicology and hygiene knowledge that may be very limited.

Manufacturing of ADCs and individual component molecules is routinely outsourced to contract manufacturing organizations. In many cases these will have appropriate knowledge of the issues, and expertise in the handling the highly toxic compounds, but the usual EHS auditing procedures should be used by potential clients to ensure that appropriate controls are in place.

The approach to exposure control is generic and applies to any hazardous material. The challenges with ADC handling in part include the differences between biological manufacturing and small molecule manufacturing, and the design for quality concepts in each case which may appear conflicting, and hence could cause confusion in project and operating teams. Where there is the potential for the manufacture of other antibodies and antibody products in the same facility as the ADC conjugation reactions, there is significant risk in protecting the antibody and conjugate production from contamination from the payload manufacture, and identifying cross-contamination control measures that are effective to the levels required may be problematic without significant segregation design.

Finally, the continued effective performance of containment systems is highly dependent on the diligence of the user teams in complying with procedures and optimized ways of working. In small molecule potent compound manufacturing facilities, it is common to dedicate user teams to reinforce continuous acquaintance with the equipment systems and operating procedures, and it is strongly recommended that similar approaches are applied in ADC payload handling activities. It is also critical to continue to routinely test systems for continued effective performance including industrial hygiene monitoring and data review.

## Impact

Exposure risk is not absolute; for a given system the risk will vary with the material handled, the process design, equipment specification, operator performance, and maintenance. It is essential with ADC payload related operations that this is well-understood and is suitably controlled as necessary. Variance of exposures and hence risk is not well understood, can be unpredictable, and the tools for detecting exposure are highly specialized and may not be readily available without research and development. Users need to recognize the uncertainties that are present and manage them accordingly. Risks need to be controlled in a logical and science-based manner, which will typically require regular quantified verification to be carried out by suitably competent industrial hygiene resource.

With the issues identified in quantified assessment of exposure levels, and the impact of even minor failures potentially leading to an unacceptable exposure risk, there is a requirement that drives a necessary strategy of redundancy and multi-faceted health and safety when handling potent compounds.

The high level of toxicity requires that control occurs close to the emission source. The very low acceptable exposure levels mean that uncontrolled emissions and contamination have the potential to cause significant effects over a very wide area due the impact of even very low levels of contamination. As a result, emissions are very difficult to control effectively and to recover once they have migrated out into the local environment. To achieve the levels of control that are required, the use of containment isolators that contain emissions at source is required.

Isolators currently represent the most effective engineered containment systems available in the industry. In the past, comprehensive containment isolator technology has been demonstrated to achieve the desired levels of containment in similar applications, albeit subject to effective design to meet ergonomic requirements of the activities carried out within, and subject to suitable containment performance testing.

With highly hazardous materials such as ADC payloads, such performance verification should reflect the possibility of failure modes not normally identified in potent small molecule facilities, and testing regimes should be designed to identify such failures and ideally their cause and frequency of occurrence. The continued ongoing re-verification of performance will need to be more frequent than might be considered normal in potent small molecule operations due to the inability to detect small but toxicologically significant failures with materials of such toxicity.

As a result of the concerns about potentially intolerable exposures through minor failures or variations in operation compliance with best practice procedures, as well as the near impossibility of identifying their occurrence in anything like an acceptable timescale to avoid risk of injury, it is appropriate to use supplementary PPE including disposable gowning and gloves, and require the use of powered air purifying respirators (PAPRs) to supplement the use of engineered containment in normal operation. Where such PPE is employed, it is essential to provide the ancillary facility components required to ensure the equipment is effectively used, including suitably located storage, personal and equipment decontamination, and change facilities.

In addition, to complement sampling and analysis within the facility to identify exposures, medical surveillance of staff health to determine whether a change in exposure profiles may be occurring should be in place. Medical surveillance should not be considered the same as biological monitoring where the specific molecule of concern is measured in tissue, blood or urine, but rather studies of basic health history and reproduction health history, including a routine general health examination and specifically defined tests for the effects of the materials in use (not the drugs in the system). Such tests might include, for example, regular breast examinations for men working with estrogens and standard blood counts for workers handling oncology drugs. Trending would be done in these programs to determine if the overall health of the working population is maintained or degrading.

## Future Trends

Novel processing methods such as continuous processing and ultra-small scale synthetic chemistry may present options to reduce emissions, though these are unlikely to reduce issues with the dispensing of isolated payload powders for example. The use of continuous methods will reduce the inventory of material present in a production system but, at this time, it is unclear to the authors that effective technology or process understanding is available to prepare effective solutions. This may change as the technology and capability for very small-scale complex processes improves.

Cytotoxic materials are of crucial importance for the effectiveness of ADCs currently being developed for oncology targets. While the current range of payload molecules presents significant challenges for contained safe handling, there are emerging plans in the industry to develop even more potent and toxic molecules to counter the reduced effectiveness when only low binding numbers can be achieved. While of potential significant benefit to the patient, such increased toxicity presents an increasing risk to workers.

Figure 4 Isolator installed for ADC payload handling

Source: Carbogen Amcis

One potential implication of this drive for ever more potent agents is that it may, in time, lead to the development of molecules which cannot be shown to be effectively controlled by any current portfolio or combination of control methods including engineered containment, PPE and worker medical surveillance. As such, there may in reality be a 'sweet spot' of toxicity where the material exposures associated with development and manufacture can still be effectively controlled while maintaining sufficiently high levels of potency to create effective ADC drugs in most applications. Whether this sweet spot has been reached already, or enhanced control regimes involving the use of segregated automated facilities might be developed that allow more toxic payload development and application, is a question under review by safety professionals and engineers working in the area.

## Closing Messages

ADC payloads provide an industrial hygiene challenge rarely seen previously in the biologics industry, potentially affecting organizations which may have limited previous experience in the safe handling of high hazard materials.

The high toxicity of the materials handled does not allow the common argument that the presence of relatively small quantities mitigates the risk of exposure to an acceptable level; the toxicity is such that even tiny emissions potentially represent significant risk to users. Against this, emotional toxicity-based responses should give way to quantified assessments based on the risk of exposure. Other areas of the pharmaceutical industry have developed robust, systematic, science-based approaches to handling such molecules, and this knowledge can be transferred to deal with the specific issues associated with the handling of biological materials.

Users need to comprehend and understand the basis of safe exposure levels for all components of ADCs based on toxicology, the profile of exposures by all routes, and the impact of specific control approaches on identified exposure risks. It is important to know where such data might be found, and what to do if it is not available; typically the uncertainties inherent in assessing exposures with such highly toxic materials will mean higher degrees of risk must be tolerated; this must be understood, accepted, and controlled through the use of redundancy and multi-layered strategies to overcome unidentified single system failures.

Finally, it must not be assumed that a system installed today will continue to be effective without a program of ongoing reverification of control system robustness, including equipment performance and attention to "soft" issues such as operator knowledge and performance and other human factors. ◂

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# THE MIRACLE OF SYNTHETIC INSULIN

## A biopharmaceutical success story

Leonard Thompson was 14, and he was dying. Just 65 pounds, the young teen faced the fate of all diabetic children in 1922: he would soon become comatose and die.

Insulin research and production have been at the center of developments in the biopharmaceutical industry.

At the time that Thompson lay dying at the Toronto General Hospital, Type I diabetes was always lethal.

Frederick Banting, Charles Best and their colleagues at the University of Toronto had already demonstrated that a canine pancreatic extract of insulin could treat diabetes in dogs, and they had hopes that an extract purified from ox pancreas would work in humans. Unfortunately, Thompson had a severe allergic reaction to the bovine extract, and the emergency clinical trial had to be postponed. The team worked diligently to improve the purification process and, when they tried again 12 days later, the experiment worked: the child's blood sugar levels dropped and his symptoms improved dramatically. Six more diabetics were successfully treated the following month and insulin's status as a miracle medicine was on its way to being cemented, ensuring Banting the Nobel Prize in Medicine in 1923.

Insulin research and production have been at the center of developments in the biopharmaceutical industry since then. Banting and Best sold the patent for insulin to the University of Toronto for 50 cents. The university, unable to produce the necessary quantities of the drug, entered into an agreement with Eli Lilly & Co., and in less than 2 years tens of thousands of patients in North America were being treated. Mass production required large amounts of slaughterhouse pigs, cows and horses, with as much as 2 tons of pig needed to produce only 8 ounces of insulin. The drug was produced in the same manner into the 1980s.

Along the way, researchers and industry collaborated on a number of firsts. Insulin was the first protein to have its amino acid sequence determined, in 1951-52 by Frederick Sanger, for which he received the Nobel Prize in Chemistry (1958). In 1978, Genentech used recombinant DNA technology to synthesize the human insulin gene. These recombinant DNA sequences—one for each chain of the insulin molecule—were inserted into plasmid DNA, then used to transform *E. coli*. Bacteria were induced to synthesize either one or the other of the two protein chains that when joined together formed insulin. In 1982, human insulin manufactured by Eli Lilly became the first genetically engineered pharmaceutical protein approved by the FDA. This form had the benefit of mitigating the allergic reactions diabetics experienced from porcine and bovine versions of the hormone.

Currently, recombinant DNA technology is used to manufacture tons of insulin, using either *E. coli* or the yeast *S. cerevisiae*. As well, researchers have taken the naturally occurring gene and molecule and modified it slightly to create synthetic versions of human insulin that have enhanced properties. These insulin analogs—examples include Humalog® (Eli Lilly), Levemir® (Novo Nordisk), and Lantus® (Sanofi)—have altered amino acid sequences that differ from naturally occurring insulin. These synthetic forms serve two purposes: they can improve the efficacy of insulin, rendering it longer acting or slower acting than the natural versions; and they allow a company to obtain a new patent and "evergreen" its product, thus staving off competition from the introduction of lower-cost generic alternatives (which cannot be produced until the patent expires).

The first long-acting synthetic insulin got FDA approval in 2000.

Evergreening was the focus of a recent article in the *New England Journal of Medicine*, which outlines the reasons that there are no generic insulin alternatives yet on the market. The authors worry that some of the 6 million diabetics in the US cannot afford the out-of-pocket expense of insulin, which can be $120-$400 per month. Industry insiders point out that patents offer incentives to biopharmaceutical companies to improve medicines like insulin. It will not take long to see how this plays out, as the patent on one long-acting synthetic insulin expired almost a year ago and a biosimilar version has been approved in Europe.

We have progressed from a time when one life was saved through groundbreaking research—with regular injections, Leonard Thompson lived to be 27 before succumbing to pneumonia—through a half-century of insulin production requiring massive amounts of animal material, to a highly efficient means of purifying synthetic insulin. Hand in hand, it is scientific research combined with the mass production and distribution capabilities of the biopharmaceutical industry that has improved the lives of diabetics worldwide.


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