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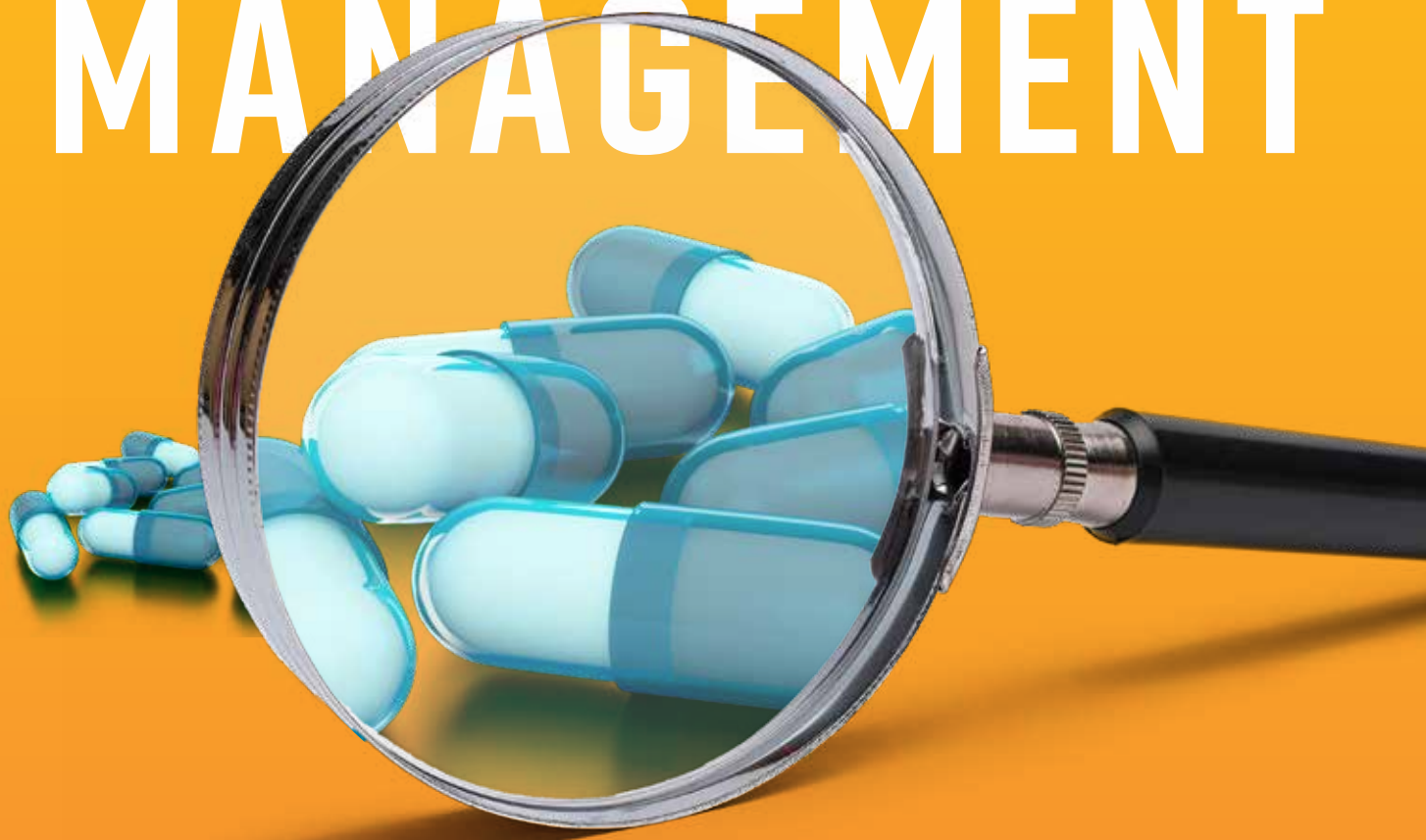
RISK MANAGEMENT



Managing Risk in Single-Use Technology

Interpretation of Variance Components for Blend and Content Uniformity

SPECIAL SECTION: 2019 ISPE Annual Meeting & Expo

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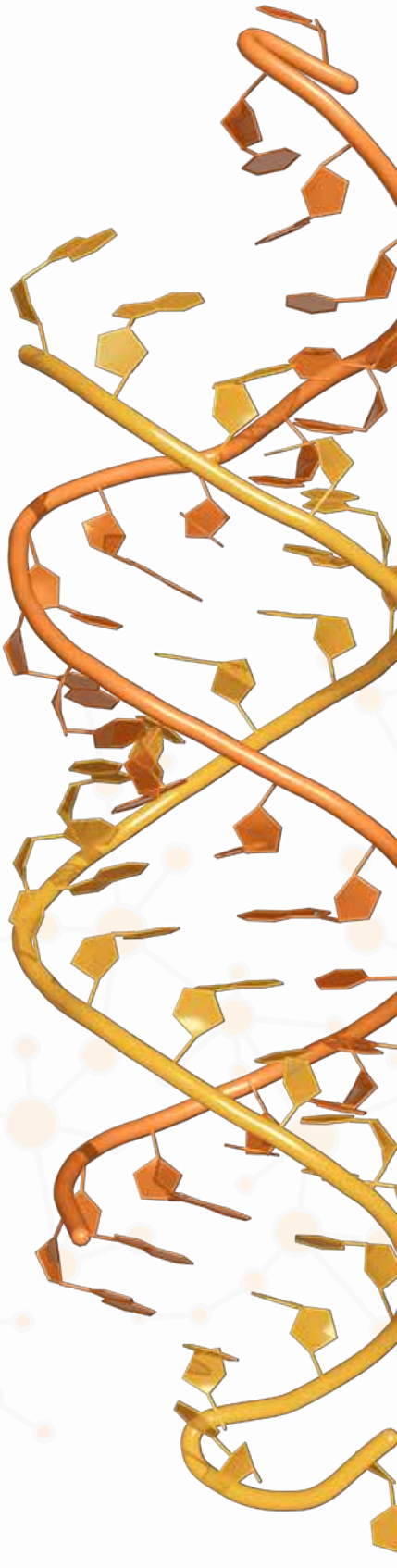

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14

RISK MANAGEMENT IN SINGLE-USE TECHNOLOGY

Risk management is pervasive throughout the biopharmaceutical industry. It is an important factor during the implementation of new equipment or procedures into an operation. Likewise, risk management is also key when assessing the impact of changes. When doing a root cause analysis, evaluation of the risks becomes central to define the potential solutions to the problem analyzed and to eliminate the contributing cause. This article expands on a chapter addressing risk management in single-use technology in the *ISPE Good Practice Guide: Single-Use Technology.*

CORRECTIONS: July-August 2019 *Pharmaceutical Engineering*

Due to a technical error, the URL for the online-only Appendix to "Application of the SOC 2+ Process to Assessment of GxP Suppliers of IT Services" was misprinted in the print edition of the magazine. Access the article at https://ispe.org/pharmaceutical-engineering/july-august-2019/application-soc-2-process-assessment-gxp-suppliers Then scroll to the end of the article to DOWNLOAD APPENDIX: https://ispe.org/system/files/magazine-issues/PE%20SOC%20Table%20v2-july-aug-2019.pdf

Figure 2 in "Accelerated Pharmaceutical Product Development, Registration, Commercialization, and Life Cycle CMC Lessons, Part 1" was incomplete. The complete Figure 2 is at https://ispe.org/pharmaceutical-engineering/july-august-2019/accelerated-pharma-product-development-registration

ON THE COVER The ever-present challenge of exploring and assessing risk in pharmaceutical manufacturing is represented by the symbol of the magnifying glass.

FEATURES

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SPECIAL SECTION: 2019 ISPE ANNUAL MEETING & EXPO

This special section looks at what's coming up at the 2019 ISPE Annual Meeting. It also features the voices of first-year Travel Grant recipients who attended last year's Annual Meeting courtesy of the ISPE Foundation and offers a look at the 2019 Facility of the Year Award (FOYA) category winners and honorable mentions.

DEPARTMENTS

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By Jim Breen

A Year of Change

As I write my last Chairman column for *Pharmaceutical Engineering*, I reflect on what has happened over the past year globally and within ISPE. The pace of change in the industry has accelerated and will continue to accelerate with new technologies and business models being deployed.

Over the past year, I have had many opportunities to visit ISPE Chapters and Affiliates, allowing me to see the true impact and value of ISPE and establish new friendships around the world.

We are looking forward to a very successful 2019 ISPE Annual Meeting & Expo in Las Vegas and the announcement of our new ISPE Strategic Plan, which will continue to build on our work in the last few years, with added focus on important future trends of the industry. The future is extremely bright and will require all of us to be agile and in a constant learning mode to keep relevant with the pace of changes and technology in the industry.

THE ROAD AHEAD

The theme for this issue of *Pharmaceutical Engineering* is Risk Management. We have all been involved in risk assessments at work and understand the importance of these tools, but have you considered managing the risk—or opportunities—in your own career associated with the speed of change in the industry? Consider how you can keep your skill sets relevant to today's market needs and the workforce of the future.

ISPE is well positioned to help you manage the opportunities ahead by facilitating industry collaboration, identifying future trends, and preparing you via training, seminars, and conferences.

New technologies such as cell and gene therapy and corresponding business models are coming to market to improve patient lives. ISPE will remain an avenue for industry collaboration and a place where members can constantly update their skill sets to participate in these new areas of growth.

MOVING ON

Thanks to the entire ISPE International Board of Directors for their support, engagement, and constant focus to improve our Society and help all members further their careers while keeping the industry focused on improving patients' lives. I want to especially note the devotion of the ISPE Executive Committee, as they are a fantastic team to work with on critical issues affecting our industry. Thanks to the ISPE staff under the leadership of John Bournas, ISPE President and CEO. I wish all the best to the International Board members who will be assuming new roles at the Annual Meeting. I know they will do a fantastic job leading ISPE into the next decade.

When I was installed as Chairman in October 2018, I challenged everyone to get involved in ISPE in whatever capacity possible, whether in a chapter, affiliate, committee, Community of Practice (CoP), or other role. I continue to challenge everyone to become involved, so together we can have the most impactful Society in the industry.

Jim Breen is 2019 ISPE International Board of Directors Chair; Vice President, Lead Biologic Expansion, Janssen Pharmaceutical; and Adjunct Professor at Drexel University. He has been an ISPE member since 2000.

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LeAnna Pearson Marcum

NETWORKING IN A DIGITAL AGE

In a world dominated by social media and online profiles, the art of getting to know someone has been transformed. So, in this age, when you can connect with someone by "swiping right" on a dating app, how do you build a professional network? Face-to-face interactions remain a great starting point. Therefore, whenever I attend a conference or other professional event, I make sure that I am rested and ready to network.

Networking is not something that came to me naturally. It is a skill I have honed throughout my career, and I will likely keep working on it as my role changes. Below are some of my networking tips, which focus on the prep work, in-person work, and follow-up.

PREP WORK

For any conference or meeting, ask yourself ahead of time, "What do I want to get out of this networking event?"

To come up with your game plan, think about the size and length of the event. Your strategy for a 40-person meeting will be different from your strategy for a conference attended by 4,000. If you're going to a single-night event, make sure you set at least one goal and achieve it! If you're participating in a multiday event (these can be exhausting), you might set two or three goals to achieve. Goals may be as simple as meeting someone from your dream company, talking with a particular speaker, or connecting with five new people.

Once you've set your goals, do your homework so you're ready to accomplish them. Exhibition halls are daunting even for the most skilled navigators, and you will be amazed at how long talking to just five vendors can truly take. Knowing that it's easy to get distracted, I like to plan ahead of time where I will go based on the people I want to talk to.

As part of your prep, use social media to your advantage. Find out who will be tweeting from the event and what LinkedIn posts there are, and retweet or follow participants. Of course, use good judgment to make sure that your professional self is present when you're online.

Finally, plan your schedule, making time to meet new people. At a large conference or networking event, it is so easy to fall into hanging out with your friends or other people you know. I try to plan at least one evening or event where I am not spending time with a friend or colleague. This was a tip I was given a long time ago, and it was very hard for me to follow, even though I'm an extrovert. If you have someone you see as mentor, ask them what after-hour events they recommend. If they invite you along, accept the invitation!

IN-PERSON INTERACTIONS

While networking, remember: The easiest thing to talk about is the person you are talking to. Just let the other person speak. When I was starting out, I found this advice to be hilarious, but it is so very true.

When I find myself wanting to meet someone but am unsure of what to ask them, I keep a few "loaded" questions on hand:

- How did you get into this field or job?
- What is something about your job that still surprises you?
- Is this your first ISPE (or other) event? Follow up by asking them about the other events or how long they have been with ISPE.
- What is your favorite thing about this city? This is a great question for big conferences held in cities that are fun to explore—if there is something everyone likes to talk about, it is having fun.

As you network, be in the moment! This is real life, so shake hands, make eye contact, and don't fidget with your phone or watch. I can't tell you how rude and disrespectful you will seem if you are only partially engaged. It makes the person feel like you are not interested in them, and that can create a lasting impression you don't want to make.

Do not be afraid to talk to anyone. Yes, you will meet people with intimidating titles. But guess what? They are people just like you, and at some point, they too were new to networking and meeting people they admired. So, instead of being afraid, be respectful and say "hi" to them. You never know where this encounter might lead.

FOLLOWING UP

A key to networking is remembering your connections. I like to ask new acquaintances for a business card. Then, *after* I finish my conversation, I make a few quick notes on the back of the card to help me remember them and them remember me. This way, when I email them or connect with them on LinkedIn, I can say, "It was so great hearing about your rock climbing adventures in Ireland at the Affiliate meeting. I hope we can stay in touch, and I look forward to hearing about your next adventure." This shows them that I truly want to connect with them and they are more than a business card to me.

When following up, don't wait too long—but don't be too eager. After a long conference, I am zonked; I am lucky if I can spell my own name and board the correct flight home. I typically wait about a week after the event to connect. This gives me time to sift through my inbox (because work and life never stop) and digest the whole conference experience.

After you first connect, reconnect. I always appreciate the individuals who reach out and ask how I am doing. I never realized the value of these types of messages until I received some myself. Now I make it a point to check in with others from time to time. By taking just the few moments to see how a connection is doing or what is new in their job, you let them know they are not just another name in your contacts list.

> For any conference or meeting, ask yourself ahead of time, "What do I want to get out of this networking event?"

LeAnna Pearson Marcum is a QAV Manager with bluebird bio in Durham, North Carolina, and the 2019–2020 ISPE International Young Professionals Chair. She has been an ISPE member since 2009.

STRONG LEADERSHIP FOR UNCERTAIN TIMES:

Jon Youles and the ISPE United Kingdom Affiliate

By Mike McGrath

In his 17 years as a member of the ISPE United Kingdom Affiliate, Jon Youles has worn many hats, including Editor for the newsletter, Chair of the Southern region's committee, and Secretary and Vice Chair of the Affiliate. Now, as Chair of the Affiliate, he leads an engaged membership that is thriving even as the Affiliate and the UK pharmaceutical industry face uncertain times.

STEPPING STONES

Originally from Lytham St Annes, a small resort town in the northwest of England, Youles studied mechanical engineering at the University of Salford in Manchester. He was introduced to the pharmaceutical industry a few years into his career. "I started out working as a project engineer within a manufacturing factory not related to the pharmaceutical industry," he explained. "Then, by virtue of moving into sales of mechanical process equipment at Hosokawa Micron, I became involved in pharmaceuticals."

It was during his time at Hosokawa Micron Ltd. that Youles first came into contact with ISPE. "I attended the ISPE United Kingdom Affiliate Annual Conference in Bournemouth in November 2002," he said. "I got to chatting with a few committee members, and shortly following, I attended the Affiliate's annual general meeting, which—I will be honest—I didn't realize was mostly about the formality of electing officers. And as often happens when you turn up young and eager, I was asked if I wanted to become part of a committee. I said, 'Absolutely, I can do that,' and I joined the Southern region's committee and got really absorbed in the process and the social networking benefits that you get from being active within an ISPE group."

The ISPE United Kingdom Affiliate was established in 1988 and currently serves around 900 members. It is divided into four regions—Southern, Central, North East, and North West—each of which has its own organizing committee. The Southern region has the largest number of members.

Jon Youles, Chair, ISPE United Kingdom Affiliate

Once initiated into the ISPE community, Youles became more active within the Affiliate's Southern committee, editing the newsletter, organizing evening seminars, and running much larger events. Youles called these roles stepping stones in his advancement within the Affiliate. By the time the ISPE United Kingdom Affiliate Annual Conference came back to Bournemouth in 2006 (the conference rotates through the Affiliate's four regions), Youles was the Chair of the Southern region's committee.

"That 2006 meeting was my first experience of chairing the conference and my first time standing up and giving a short address to the 450 guests at the awards dinner," Youles explained. "Being in this role was terrifying, and it is something that still makes me nervous today."

Youles subsequently held the positions of Secretary and Vice Chair of the Affiliate before becoming the Chair. Although these positions are normally held for 2 years, Youles is currently in his third year as Chair. He expects to hand over the office to Vice Chair Pat Drury in 2020.

Youles currently resides in the southern part of the UK in a town called Newport Pagnell. He is the Managing Director of Ytron-Quadro (UK) Ltd., a small process equipment and manufacturing solutions organization serving the food, cosmetics, and pharmaceutical sectors in the UK. He has been with Ytron-Quadro for the past 14 years.

LIFE OUTSIDE OF WORK

In his spare time, Youles, 48, is quite adventurous. Since his university days, he has been into what some may call "extreme" sports, including rock climbing, paragliding, snowboarding, and

mountain biking. On one notable excursion, he cycled from the southwestern-most point to the northeastern-most point in the British Isles. Along the way, he diverted his path to undertake a "three peaks challenge," which involved walking up the three highest mountains in the UK: Snowdon in Wales, Scafell Pike in England, and Ben Nevis in Scotland. The total distance of that remarkable trip was about 1,100 miles (1,770 km).

Youles proudly noted that he's never had any major incidents in 30 years of sporting activities; however, he recently experienced what he described as an "unplanned dismount" from his mountain bike, causing him to go over the handlebars and land on his shoulder. "Unfortunately, I broke my collarbone," he said. "So, I am recovering from surgery and I have a metal plate in my right shoulder, just holding everything together."

While he has taken some time off to recover, Youles noted that the pain is manageable and he is looking ahead to participating in upcoming ISPE United Kingdom Affiliate events.

PROVIDING MEMBER BENEFITS

In his role as Chair of the ISPE United Kingdom Affiliate, Youles keeps the focus on providing interesting and engaging events to support his diverse membership throughout the country. The UK's pharmaceutical industry employs more than 73,000 people and contributes £30.4 billion to the British economy, including £4.2 billion in research and development expenditures [1]. Within the Affiliate, representation comes from every area of the pharmaceutical sector, including manufacturing, suppliers, and engineering support organizations, as well as the Medicines and Healthcare Products Regulatory Agency (MHRA).

Lynn Bryan, CoP Liaison for the ISPE United Kingdom Affiliate, speaking before an attentive audience at the Affiliate's Summer Conference, 19 June 2019.

Youles noted that the Affiliate aims to hold four to six events in each of its four regions per year. These include evening seminars, where two or three presenters speak on a topic; site tours to newly opened plants or facilities working on something of interest; and workshops where attendees can delve into a specific topic.

> "We feel that we give the most benefit to our members by providing these regular opportunities to learn about a particular topic."

"We also have a Summer Conference, which is a one-day conference typically used to either highlight upcoming guidance documents or to give an overview of newly released guidance documents," said Youles. "This year, however, we are doing an introduction to pharma because we recognize that there are a lot of individuals joining the industry who don't have a specific pharma manufacturing background. So, we are giving them a basic grounding in what it means to be involved in the pharmaceutical industry and setting the groundwork for further education. We're also looking to do more workshops, which will be in a classroom setting and potentially a hands-on practical event to give members a more in-depth level of information and knowledge sharing than we currently do with our evening events." (This year's Summer Conference was held 19 June 2019.)

The educational aspects of events and the networking opportunities can be invaluable to members. "We feel that we give the most benefit to our members by providing these regular opportunities to learn about a particular topic," said Youles. "It's not a training session; it is volunteer speakers giving good insight into the subjects that we cover. And we also give people the opportunity to network with other members, and that establishes a link where people can share ideas outside of the event."

While Youles expressed a preference for in-person events, he acknowledged the emerging potential of virtual meetings. "We are starting to move toward that a bit more because we appreciate that time is at a premium for the members, and actually getting out and visiting a site can be very difficult to achieve," he said. "So, we're looking into how we can also deliver the same kind of content in a prerecorded or live webinar format."

LOOKING AHEAD

Clearly, the largest concern for the UK pharmaceutical industry—and, by extension, the ISPE United Kingdom Affiliate—is the country's imminent exit from the European Union. "In terms of what Brexit will mean for the Affiliate, it will really come down to what the impact is on manufacturing within the UK," said Youles. "At the moment, we have a very strong and robust pharmaceutical manufacturing sector. I believe it is one of the highest contributors to GDP of any manufacturing sector. My hope is we will keep this pharmaceutical presence, because, if we don't, we'll have problems, both at the ISPE Affiliate and, more importantly, for the UK as a whole. I am hopeful and confident that it will work out, but I couldn't confidently predict how."

With regard to the ISPE United Kingdom Affiliate, Youles credited its ongoing strength to the volunteers who help organize the events that members find so engaging. "The activities of the Affiliate are organized entirely by volunteers on the committees," he explained. "People sometimes assume that we are paid to do this, and we're not. A lot of people give up an enormous amount of time doing an amazing amount of work, and I want to acknowledge and recognize them and their outstanding contributions."

Reference

1. Skirmuntt, M. "Biotechnology & Pharmaceuticals." Great Place to Work website. Published May 2017. https://www.greatplacetowork.co.uk/assets/Uploads/Biotechnology-Pharmaceuticals-Industry-Insight-FINAL-May-2017.pdf

About the author

Mike McGrath is a freelance writer and corporate communications consultant. For the past 15 years, he has helped organizations in the aerospace, transportation, telecommunications, and pharmaceutical industries develop their digital and print communications strategies. He has been a regular contributor to *Pharmaceutical Engineering* since 2015.

Quick facts about the ISPE United Kingdom Affiliate

Founded: 1988

Region: United Kingdom

Membership: Approximately 900

Officers

Chair: Jonathan Youles, Ytron-Quadro (UK) Ltd.

Treasurer: Philip Hill, Fulkers

Secretary: Bruce Williams, Williams Process Ltd.

Past Chair and North East Chair: Peter Dodd

Vice Chair and North West Chair: Pat Drury, Northern Valve and Fitting Company Ltd.

CoP Liaison: Lynn Bryan, Ballygan

Central Chair: Shaun Baker, BW Packaging Systems Ltd.

Southern Chair: Nick Kesterton, Rockwell Automation

Membership Chair: Phillip Richardson, AstraZeneca

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RISK MANAGEMENT IN SINGLE-USE TECHNOLOGY

By Pietro Perrone, PhD, PE, and Christopher J. Smalley

Risk management is pervasive throughout the biopharmaceutical industry. It is an important factor during the implementation of new equipment or procedures into an operation. Likewise, risk management is also key when assessing the impact of changes. When doing a root cause analysis, evaluation of the risks becomes central to define the potential solutions to the problem analyzed and to eliminate the contributing cause.

Risk management during implementation of single-use technology (SUT) typically involves the new equipment and, in some cases, changes to an existing process. Even if process changes are not factors during the initial implementation of SUT, they may arise later in the life cycle of the product. Therefore, subsequent risk management in response to changes should be an important consideration during the implementation process.

This article is an expanded version of the Chapter 4.2, "Risk Management," in the *ISPE Good Practice Guide: Single-Use Technology* [1].

WHEN AND WHY IS RISK MANAGEMENT IMPORTANT?

The flexibility demanded by today's biopharmaceutical industry and the flexibility of SUT to meet these demands are major reasons to manage risk as early as possible in the implementation process. Early risk management provides a foundation that maximizes flexibility while mitigating risks that depend on the specific path followed within the flexible platform. An effective risk management strategy uses assessments early in the projects and facilitates the transfer of appropriate measures that minimize risks via the quality agreements made with SUT suppliers. (Details on the content of quality agreements can be found in Chapter 2.5, "Supplier Qualities and Audits," in the *ISPE Good Practice Guide: Single-Use Technology* [1].)

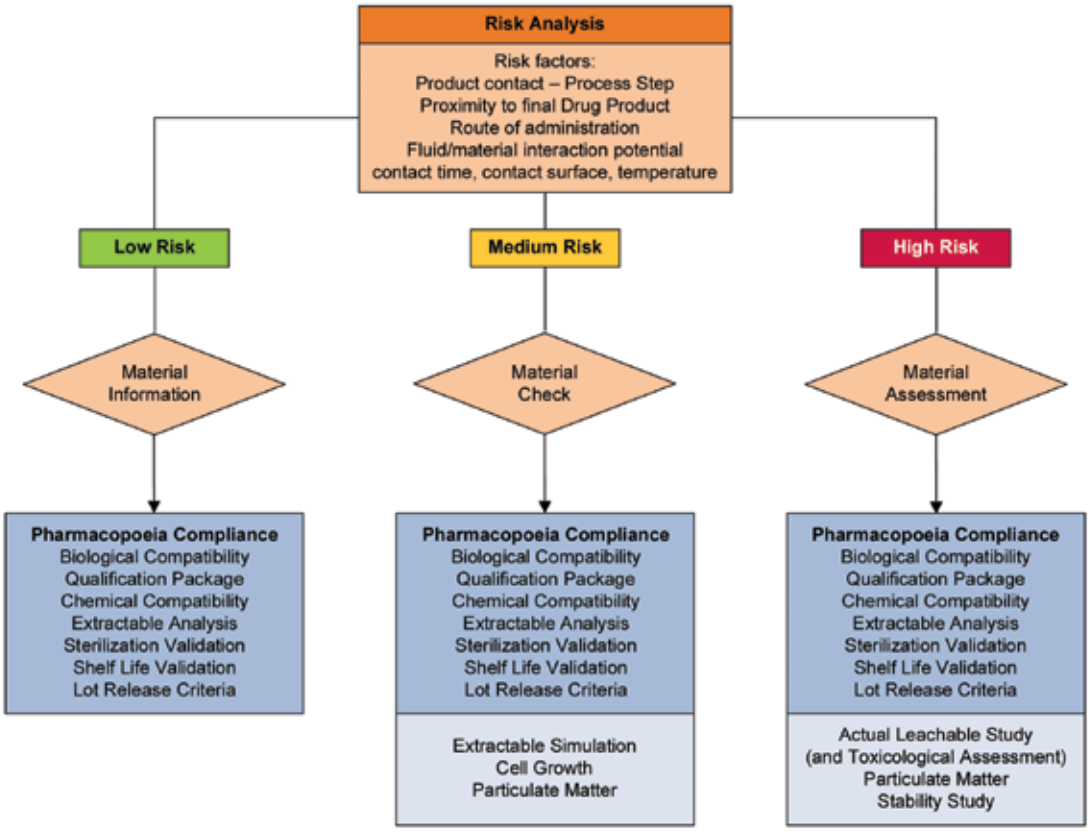
Sources of risk to be assessed during implementation of SUT include:

- Material compatibility with the finished SUT
- Availability of products to meet production schedules
- Changes in source materials once the SUT is qualified
- Leaks or performance issues
- Inventory fluctuations and shelf life

Given the rapid development of new products in the biopharmaceutical industry and the ongoing evolution of the SUT, changes will be inherent in any application (circumstances of use). Changes can be relatively minor or very disruptive. See Table 1 for examples of each category of changes. To help minimize risk, quality agreements should include requirements that the end user will be immediately notified of any sign of major or disruptive changes. Additional requirements in the quality agreements should be the defined actions and the associated timelines that the supplier shall meet for any changes.

Risk assessments should also be based on the proximity of the component contact to the final drug product and the impact on patients. Figure 1 presents a decision tree for establishing this impact and the level of documentation required to confirm that risk is minimized. Examples of each risk level based on the decision tree are:

Figure 1: Decision tree for regulatory documentation requirements when using plastic packaging material for drug substance use and storage [1 (p. 84)].



- Low risk: Buffer preparation upstream of the process
- Medium risk: Product transfer at an intermediate step
- High risk: Final fill of a parenteral solution

Risk management should be applied throughout the implementation of SUT. The guidance from ASTM E2500-13 details the role and interrelationships of risk management as part of Good Engineering Practice [2 (p. 4, Figure 1)]. Risk assessments should be conducted at the beginning and multiple subsequent points of the implementation program. To be effective, risk management programs require involvement from top management and support across the entire organization.

One of the guiding principles of ICH-Q9 is: "the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk" [3]. The *ISPE Good Practice Guide: Good Engineering Practice* further encourages biopharmaceutical companies to apply the appropriate level of risk management to provide cost-effective solutions. That guide classifies risk management as a core activity that should balance risk against benefits and that risks should be reduced to acceptable levels [4].

It is recommended that the risk management program include, at a minimum, a failure mode and effects analysis (FMEA) done at the beginning of the implementation to address at least the potential risks. Refer to the *ISPE Baseline® Guide: Commissioning and Qualification* [5] and ASTM E2500-13 [2]. Table 2 identifies notable tools and resources to assess risk.

CATEGORIES OF RISKS

The sources of risks identified earlier in this article can be addressed in a comprehensive risk analysis. Clarification of each type of risk can help to identify and structure the criteria to include in the risk assessment.

Risks due to leaks or performance issues usually tend to surface once the single-use product is applied in manufacturing operations. Because many connections occur in single-use assemblies and a significant amount of handling can occur during product installation and use, it is important to estimate this risk early. Historical information from the supplier relative to failure rates and trends will help assess this risk.

Experience with the single-use product during test programs can also be used to assess the risk if the test conditions were conducted in a controlled manner. Evaluation of single-use products during test programs executed by the user can present variable and unusual conditions to the single-use products as the application (circumstances of use) is developed. Therefore, leaks and performance issues that occur in this phase should be adjusted for the more controlled conditions that are present in a manufacturing cGMP environment. Leaks or performance issues discovered in the user's test programs should be used to refine manufacturing standard operating procedures (SOPs) or to initiate design changes in single-use assembly and/or shipping containers that minimize this risk. The level of adherence to refined SOPs in manufacturing environments will typically align with the predictability of risk for leaks or performance factors.

Table 1: Changes that contribute to risks and should trigger a risk assessment.

Change Category	Examples of Changes
Maintenance/improvement changes	Operational improvements Change in drawing format or documentation Different storage location Change in transit route
Major disruptive changes	Change in material of construction or formulation New manufacturing location Change in component dimensions Change in packaging of single-use component/assembly Different single-use product supplier New sterilization supplier/location

Table 2: Selected tools and references used to evaluate the level of risk.

FMEA
Fault tree analysis
ICH Q9 [3]
ASTM E2500-13 [2]
ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment [6]
ISPE Baseline® Guide: Commissioning and Qualification [5]

Risks due to availability of single-use products to meet production schedules depend primarily on the reliability of the supplier. These risks also must be minimized for smooth operations. Keeping a high level of inventory can offset some availability risks. However, keeping a high inventory is costly, and this approach can cause large inventory fluctuations when inventory needs to be discarded due to shelf-life constraints.

The physical size of the single-use assembly can be a risk factor to consider. The larger assemblies have characteristics that can increase risk. These include:

- They have higher surface contact area.
- They contain larger volumes of liquid.
- They have more connections.
- They are more complex.
- They are heavier.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These factors can make it more difficult for the operators to handle the assemblies from the package to their installation into the process/operation.

Although all risk factors need to be evaluated in the assessment, one of the more important risk categories for SUT involves materials. This is because the single-use components and assemblies are often customized and implemented in new applications. Therefore, the rest of this article focuses on a consistent compliance approach to demonstrating suitability of a given single-use system (SUS) for its intended use in manufacturing. Different applications of SUT are guided by user requirements, which guide the total requirements for design, selection, qualification, procurement, and implementation considerations.

RISK ASSESSMENT APPROACH

The risk assessment model presented in the *ISPE Good Practice Guide: Single-Use Technology* involves the calculation of a risk score representing the potential risk of the process contact materials (PCM) that are present in the SUS [1]. For a given risk category, additional required in-house qualification should be performed, or leveraged from existing data, and documented. Supplier and, if necessary, in-house qualification data packages are required to demonstrate suitability of the PCM for its intended use. Where a prior history of using SUT has been documented, a comparability protocol can be considered in addition to leveraging the existing data for qualification attributes.

The steps for the risk assessment model are:

- Step 1: Identify user requirements for the PCM.
- Step 2: Obtain PCM validation data package from the supplier.
- Step 3: Perform risk assessment.
- Step 4: Execute in-house qualification studies required based on the risk score.
- Step 5: Perform risk mitigation.

The steps to qualifying PCMs for manufacturing applications include identifying specific supplier qualification requirements, which are drawn from the following 15 critical qualification attributes (full descriptions of these 15 attributes are provided in Appendix 4 of the *ISPE Good Practice Guide: Single-Use Technology* [1]; other qualification attributes specific to an application may be added):

- Biocompatibility testing
- Mechanical properties

Table 3: Risk classification based on route of administration (risk factor A).

Risk Classification	Route of Administration	Examples of Drug Formulation
High (risk score = 10)	Inhalation/nasal	Inhalation aerosols and solutions Nasal sprays Nasal aerosols Inhalation powders
	Injection (>10 exposures per life)	Injectable suspensions and solutions Sterile powders; powders for injection
	Ophthalmic (>10 exposures per life)	Ophthalmic solutions and suspensions
Medium (risk score = 5)	Injection (≤10 exposures per life)	Injectable suspensions and solutions (e.g., vaccines) Sterile powders; powders for injection
	Ophthalmic (≤10 exposures per life)	Ophthalmic solutions and suspensions
	Internal application	Implants Rectal/vaginal creams and solutions
Low (risk score = 1)	Transdermal	Transdermal ointments, creams, lotions, and patches
	Internal irrigation	Nasal rinse solutions
	Topical	Topical lotions, creams, solutions, and suspensions Topical powders Topical aerosols
	Oral	Lingual aerosols Oral solutions and suspensions Oral powders Oral tablets Oral capsules (hard and soft gelatin)

- Gas transmission properties
- Gompendial physicochemical testing
- Animal origin control
- Total organic carbon analysis
- pH and conductivity
- Extractables and leachables
- Chemical compatibility
- Protein adsorption studies
- Endotoxin testing
- Sterilization (irradiation)
- Container closure integrity
- Particulate testing
- Calibration of embedded instrumentation

Some of these attributes, such as animal origin control, may become core requirements for a firm. Others, such as calibration of embedded instrumentation for bioreactors, may be added depending on the application.

In advance of conducting qualification activities, it is recommended that an audit of the supplier be completed. This audit can determine in advance how well the PCM might perform against applicable elements for qualification. Once the results of the risk assessment are known and the elements required to be taken into consideration for qualification have been identified, PCMs from appropriate suppliers are chosen for qualification activities.

If qualification results are inconclusive or variable between PCM batches, additional controls may need to be placed on the PCM as part of the supplier manufacturing process or when PCMs are received by the end user for manufacturing. The qualification results ultimately lead to the incoming requirements as part of the normal quality acceptance of PCM batches.

Other requirements that should be taken into consideration include:

- Establish the expiration dates for the PCM, with sufficient justification and supporting documentation.
- Provide storage conditions requirements necessary to support the expiration date.
- Determine the applicability of any preuse tests.
  - In addition to any incoming PCM testing, confirmation of the quality of the PCM may be needed when it is installed or just prior to use.
  - In the absence of specific guidelines, an evaluation and justification should be made to establish any requirements.
- Determine the need of any postuse tests.
  - There may be instances where there is a regulatory requirement to confirm integrity postuse (e.g., vent filters).
  - In the absence of specific guidelines, an evaluation and justification should be made to establish any requirements.

RISK ASSESSMENT—CALCULATION OF RISK SCORE

The purpose of the risk assessment is to determine the extent of in-house qualification required according to a calculated risk score for each PCM. The risk assessment model presented here takes into account the potential risk to product quality and patient safety. Certain risks should be mitigated by supplier quality systems and upfront evaluation such as chemical compatibility and USP Class VI certification [7]. Supplier audits should be performed to ensure full traceability of the PCM to its raw materials.

In advance of conducting qualification activities, it is recommended that an audit of the supplier be completed. This audit can determine in advance how well the process contact materials (PCM) might perform against applicable elements for qualification.

As an example, a risk assessment model may be formulated to calculate the risk score as follows:

Risk Score = A × B × C × D

Where:
A = Route of administration
B = Proximity to final product
C = Contact time
D = Surface area–to-volume ratio

This risk assessment model can be applied to assess the relative risk of an individual PCM and to determine the amount of in-house qualification data required. For each risk factor, the score can be classified as high (risk score = 10), medium (risk score = 5), or low (risk score = 1).

Risk Factor A: Route of Administration

For the risk assessment, the following information relevant to the route of administration should be recorded:

- Product name (that the material will be used with)
- Statement of the dosage form

Table 3 lists examples of risk score assignments for routes of administration along with selected examples of drug formulation. The risk classification for the route of administration is based on the US Food and Drug Administration publication *Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics—Chemistry, Manufacturing, and Controls Documentation* [8].

Risk Factor B: Proximity to Final Drug Product

The likelihood that the PCM will have an impact on the quality of the drug product generally increases as the process moves downstream toward the manufacture of final drug product. In certain cases, such as biologics, the risk may also be high at vulnerable upstream points. Knowledge of the process, the contact materials, and the product should be applied to assign an appropriate risk level. It is therefore important for the validation team to collaborate with the formulation team to understand these sensitivities and requirements. Table 4 lists examples of risk score assignments based on proximity to final product.

The likelihood that the PCM will have an impact on the quality of the drug product generally increases as the process moves downstream toward the manufacture of final drug product. In certain cases, such as biologics, the risk may also be high at vulnerable upstream points.

Risk Factor C: Contact Time

Contact time is the total exposure time that the PCM is in contact with the product (solution). If the solution just flows through, then the contact time is short and can be rated as low risk. Contact times would likely be long during the down/dwell time when the solution is in static contact with the PCM, or during the entire mixing period where solutions are agitated in the mixing tank/bag. If the solution is flushed after the stoppage, the static time during the stoppage is the largest contributor to the contact time and can often be used to determine the risk score for contact time.

If the product is in solid phase, it should be rated as low risk regardless of the contact time. Table 5 lists examples of risk score assignments based on contact time.

Risk Factor D: Surface Area–to–Volume Ratio

The greater the ratio of the contact material surface area to the product volume (such as batch size) is, the greater the potential risk for leachables, adsorption or absorption of active ingredients or excipients, and chemical reactions with the contact material.

The worst-case surface area-to-volume ratio is a single-use product/assembly with a smaller process volume because it usually has higher surface area-to-volume ratio. The smallest batch size usually represents the worst-case scenario. The lower the volume is, the more concentrated any potential leachables would be. If the single-use product/assembly applied in the manufacturing process is large (e.g., an assembly containing ≥100 liters of fluid), using a very small amount of single-use material for testing (e.g., a 50-mL container) may not provide data usable for interpretation. A higher amount of single-use material (e.g., a 150-mL, 250-mL, or even 500-mL container) will provide better data for extrapolation to manufacturing-size single-use products/assemblies.

Table 4: Risk classification based on proximity to final drug product (risk factor B).*

Risk Classification for Risk Factor B	Proximity to Final Product	Comment/Justification
High (risk score = 10)	Manufacture of the dosage form without a dilution or purification step before the final container closure system.	Any contaminants will be transferred into the container and consumed by patients.
Medium (risk score = 5)	Compounding of the drug product that involves a dilution or purification step before filling. Production of active substances that will be >50% concentration in the final drug product.	All steps including diafiltration, purification, filtration, and/or dilution >50% will provide a synergistic effect in reducing contaminants in the final product.
Low (risk score = 1)	Production of active substances including all media and buffer preparation.	All steps before compounding will inherently have lower risk because all the downstream process steps will reduce/dilute contaminants as the process progress.

*Not all of the categories for the proximity to final product risk factor listed in this table will be used at every site (e.g., if a site only performs filling of final product, all contact materials will be high risk for that area of production).

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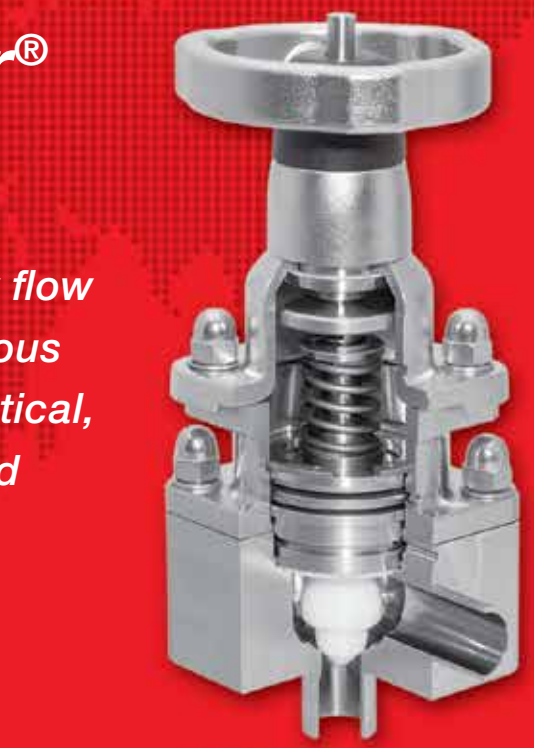

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Table 5: Risk classification based on contact time (risk factor C).

Risk Classification	Contact Time	Comment/ Justification
High (risk score = 10)	>7 days of exposure time	SUSs will be treated as an intermediate/shipping storage vessel if materials will be stored beyond 7 days.
Medium (risk score = 5)	Between 48 hours and 7 days of exposure time	Intermediate or bulk drug product may be stored in bags up to 7 days for further processing.
Low (risk score = 1)	<48 hours of exposure time	Production campaigns can be filled within 36 to 48 hours.

Table 6: Risk classification based on surface area–to–volume ratio (risk factor D).

Risk Classification	Surface Area–to–Volume Ratio	Comment/ Justification
High (risk score = 10)	>0.01 cm^2/mL	A safety factor of >15-fold relative to extraction condition per USP Class VI testing [7]
Medium (risk score = 5)	0.001–0.01 cm^2/mL	A safety factor of between 15- and 150-fold relative to extraction condition per USP Class VI testing [7]
Low (risk score = 1)	<0.001 cm^2/mL	A safety factor of >150-fold relative to extraction condition per USP Class VI testing [7]

Surface area can be calculated based on the dimension of the contact materials. For items such as gaskets and O-rings, the surface area in contact with a solution can be estimated. Overestimating the area covers the worst-case scenario.

For gases (e.g., nitrogen), the risk should be classified as low because the risk of a gas removing substances/leachables from the PCM is very low. Table 6 lists examples of risk score assignments based on the surface area-to-volume ratio.

Determination of Final Risk Level

After the calculation of the final risk score using the risk score equation noted previously (Risk Score = A × B × C × D), the final risk level is assigned as follows:

- Low: calculated risk score ≤1,000
- Medium: calculated risk score between 1,001 and 4,999
- High: calculated risk score ≥5,000

Documentation of the risk score calculation for each PCM should be included in the PCM qualification report. The final risk level can be used to determine the additional in-house qualification studies required.

EXECUTING IN-HOUSE QUALIFICATION

Based on the final risk level of the PCM, the required in-house qualification activities can be determined. Use of subcontractor services for testing may be considered. Regardless of final risk level, in-house qualification requirements should always include:

- Leak/pressure/crack verification
- Tear evaluation (for bags)
- Sterility evaluation (for sterile-supplied PCM)
- Endotoxin evaluation (for sterile-supplied PCM)
- Integrity testing (for 0.2-µm filters, whether sterilizing or for bioburden reduction)

Where the final risk level is medium (calculated risk score between 1,001 and 4,999), additional in-house qualification requirements should include:

- Sorption testing (the uptake of product components by the plastic materials) [9]
- Spallation testing (particle shedding due to repeated compression of peristaltic pump tubing) [10]

Where the final risk level is high (calculated risk score ≥5,000), additional in-house qualification requirements should include:

- pH change evaluation
- Leachables testing
- Particulate evaluation

Once the required in-house qualification requirements are identified, there are several approaches to reduce the amount of testing, such as using existing data from suppliers and in-house data, the quality-by-design (QbD) approach, paper exercises, or a combination of these methods.

Using Existing Data

In most cases, existing data from the supplier and in-house data can be utilized without the need to perform additional work. Careful evaluation is necessary to ensure that the existing data support the intended use of the PCM.

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Risk is also a consideration in evaluating supplier documentation. Only formal and official documents issued by the supplier should be admissible. Supporting data need to be provided using an appropriate format (e.g., official statement or executive summary) and registered in an adequate tracking system. A traceable formal document from the supplier should be used; use of information from a website is not recommended.

QbD Approach

The QbD approach involves using data for a higher-risk PCM to qualify the same PCM in the same or lower-risk categories. The PCM categorized as high risk can be qualified to bracket lower-risk-category PCMs if all of the following criteria are met:

- Same grade of resin and material of construction
- Same supplier/manufacturer
- Used for the same/similar drug substance, drug product, or excipient

All samples can be prepared in accordance with QbD principles to represent worse-case and bracket uses in less-severe conditions.

Paper Exercise and Combination Approaches

For certain low-risk applications, in-house qualification studies can potentially be satisfied with a paper exercise to meet qualification requirements without the need to perform testing.

A combination of approaches in one PCM qualification can be considered. If in-house qualification testing is required, the testing can be designed for an individual PCM or for a group of PCMs. It is important to first understand the advantages and disadvantages of each approach and the future implications with regard to data leveraging, material changes, and alternate supplier qualification.

RISK MITIGATION

Following qualification activities, the report conclusion should highlight any of the tests in which additional controls may need to be placed on incoming materials. If the qualification package is complete and compliant, with all acceptance criteria met and without inconclusive test results, the PCM is routinely accepted with minimal incoming test requirements. These incoming requirements should minimally include:

- Confirmation of materials (correct PCM and site of manufacture)
- Confirmation of sterility status, if applicable
- Review of the certificate of analysis (COA) for any prescribed supplier testing and certification
- Confirmation of packaging integrity or packaging configuration

If any qualification studies are inconclusive, incoming controls should be placed on the PCM. Likewise, deviations encountered

during the use or processing of the PCM may also be an indicator for placing controls on the incoming PCM.

If the material does not meet the minimum requirements, there are remediation options, such as:

- Requesting that the supplier generate the test data
- Performing in-house qualification
- Selecting another supplier
- Implementing a risk-mitigation step in the process, if possible

Risk management involves looking at all the variables and their impact. Effective risk mitigation depends on a thorough assessment of risk for all the materials. Many of the construction materials used for SUT may already be in the existing process. The materials may exist in filters, thermoplastic tubing, polycarbonate connectors, silicone tubing, or housings for sensors. Making use of this information can facilitate the risk assessment.

It is also important to understand the context of the risks. For years, the industry has used glass-lined tanks for products/processes sensitive to metal ions or their catalytic effects. An extractables study on type 1 borosilicate glass, typically used for the glass-lined tanks, may identify the presence of lead and arsenic. However, the detection of arsenic and lead in an extraction study does not invalidate the use of the glass-lined tanks. Such an extraction study is considered rather extreme due to its use of nitric acid and a reflux method. Similarly, the extraction methods for polymeric and other single-use materials can be considered extreme, and the results need to be assessed appropriately.

CONCLUSION

Comprehensive risk management relies on:

- Evaluating risk from all sources
- Including risk of all contact materials (polymeric and other components)
- Assessing risk based on impact
- Balancing risk against benefits

There are numerous publications on handling risks in biomanufacturing, including those referenced in this article. The *ISPE Good Practice Guide: Single-Use Technology* should be a primary document to use when developing a risk management program. The guide aims to provide direction for managing risk that is practical and effective.

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ACCELERATED PHARMACEUTICAL

Product Development, Registration, Commercialization, and Life Cycle

CMC LESSONS, PART 2

By Christopher J. Potter, PhD, Huimin Yuan, PhD, Nina S. Cauchon, PhD, RAC, Liuquan Lucy Chang, Derek Blaettler, Daniel W. Kim, PharmD, Peter G. Millili, PhD, Gregory Mazzola, Terrance Ocheltree, PhD, RPh, Stephen M. Tyler, Geraldine Taber, PhD, and Timothy J. Watson

This article is Part 2 of a two-part series exploring what we can learn from examples of pharmaceutical products being approved using accelerated programs. The series focuses on challenges that chemistry, manufacturing, and control (CMC) development teams may encounter when a project is given accelerated development status. In Part 1, which was published in the July–August 2019 issue of *Pharmaceutical Engineering*, we introduced key considerations and themes in general terms and highlighted future opportunities in accelerated pharmaceutical product development. In this article, we provide more detailed discussion of the considerations and themes and present several case studies.

REVIEW OF KEY CONSIDERATIONS AND THEMES

As explained in Part 1, key considerations in accelerated pharmaceutical product development include:

- Teamwork and project planning
- Control strategy
- Process validation
- Pharmaceutical quality system (PQS) readiness
- Regulatory considerations

In the following sections, we expand on these key considerations and themes.

TEAMWORK AND PROJECT PLANNING

Initial Planning of an Accelerated Development Approach

When early clinical trial data indicate a potential accelerated development designation and a decision is made to pursue an accelerated development approach, it is critical for the CMC project team working with the whole development project team to:

- Build out development scenarios necessary to accommodate the accelerated timelines, dependencies, and interactions.
- Define options for the development strategy.
- Develop filing timelines for each proposed strategy.

During this phase, the development team should review options derived from the clinical strategy (i.e., what clinical data the regulatory authority will accept, what pivotal studies and clinical data are required, and the associated timelines). The CMC project team

should discuss development and supply chain options and analyze those options in close collaboration with the impacted sites (e.g., launch and commercial sites), external partners, and, where appropriate, regulatory authorities.

The development/validation data required to support each potential filing submission should be identified. These data include critical quality attributes (CQAs), critical process parameters (CPPs), process characterization and verification studies, cleaning studies, stability studies, and so on. It is important to identify critical path activities, early regulatory engagement opportunities, and resource requirements. For example:

- Evaluate the registration lot strategy, including site selection (launch readiness planning), and supply chain considerations.
- Evaluate the control strategy, including in-process, release, and stability testing.
- Assess CMC studies proposed for deferral during review and postapproval.

All of the preceding project analysis should also include iterative risk assessments to ensure that the strategy does not adversely affect patient safety priorities (e.g., purity, immunogenicity, viral clearance, and/or biological activity), product efficacy, or regulatory commitments. Application of risk management processes should allow teams to prioritize studies necessary to ensure patient safety and consider those related to process optimization as lower priority.

A comprehensive pharmaceutical product life-cycle strategy should be devised and agreed upon as early as possible in situations where the CMC timeline is potentially constrained by the accelerating clinical program and patient needs. However, early in the development life cycle, sponsors of accelerated programs cannot be prospectively certain which matters can be successfully negotiated with regulators. Therefore, decisions should be made that allow for maximum flexibility to key components of an accelerating CMC program including:

- Remaining agile in the face of clinical changes and regulatory input.
- Planning the process development and supply chain for pivotal supply manufacture to support filing and launch activities, and to potentially supply additional clinical materials.

The outcome of the preceding analysis should be captured in a project plan and approved by the appropriate CMC and quality teams and communicated to all internal stakeholders.

Next Steps After Receiving the Accelerated Development Designation

Upon receiving the accelerated development designation from the health authority, CMC development teams should further expand the project plan and gap assessment in close collaboration with the commercial site. The gap assessment focuses on supply chain, CMC, testing, stability, validation, and cleaning, as well as overall business risks. Multifunctional and multidisciplinary development teams should lead efforts to accomplish the following:

- Perform holistic risk assessments to identify quality system/compliance challenges and proposed deferred studies, including supporting rationale, interim controls, and definition of interdependencies.
- Update the project plan to document all deferred activities, associated rationale, and dependencies.
- Work with functional area leads to develop individual functional strategies for deferred activities. Details of this work will depend on the complexity of the specific issues to be addressed.
- Identify the need for bridging protocols. The content of such protocols will depend on the level of product and process knowledge, as well as the timing of the accelerated development designation (e.g., when launching at a smaller scale or using clinical material for commercial distribution).
- Connect with the clinical teams to identify opportunities to leverage clinical bridging studies.

In parallel with the accelerated development activities, the regulatory team should develop a global filing strategy, identifying expectations for comparability studies and supportive data required to meet those filing requirements. For an accelerated development designation, it should be anticipated that some CMC and Good Manufacturing Practice (GMP) activities typically completed prior to filing may be deferred and completed after filing, either during the preapproval inspection (PAI) or postapproval, based on completed risk assessments and control strategies, which, where possible, are developed in agreements with regulatory authorities.

This overall quality system strategy and rationale, including risk management planning, should be documented in a project plan and in function-specific project plans as needed. The project plan helps ensure transparency with regard to the various milestones and gating requirements.

The deferral approach should also be discussed with each health authority to reach a consensus during the accelerated development. The results of these discussions may impact the filing strategy or development plan.

Additional bridging/comparability studies may be required to address gaps identified during the risk assessments (e.g., releasing clinical material for launch, launching out of a clinical facility with transfer to commercial scale). Such studies may also be needed to update the control strategy as new knowledge is gained later in the product life cycle.

Resource planning is an important component of accelerated development planning. For many projects, the same personnel may be responsible for the following:

- Ongoing development activities
- Plant support
- Postapproval change management
- Regulatory filing/submission activities, including negotiation and responses to requests for information from various health authorities

If possible, separate teams should be designated for some of these activities. In addition, development work may be needed at multiple sites (i.e., clinical site vs. commercial site, drug substance site vs. drug product site), which puts additional constraints on the development team.

Accelerated development pathways are not well defined in many global regions. However, once initial marketing applications have been submitted with an accelerated development pathway in a major market, markets in the rest of the world may push to accelerate their submissions. This puts additional pressure on resources to manage the preparation and submission of global dossiers.

Teams taking a full life-cycle approach may wish to consider the advantages and disadvantages of the following product launch strategies:

- Using the fastest possible regulatory path and product launch with a comprehensive life-cycle plan for subsequent postapproval introduction of an optimized process. This approach could translate to launching with a "first-generation" process or product that potentially involves a higher cost of goods, more waste, inefficient processes, and decreased patient acceptability (e.g., multiple dosage units rather than a single unit, or a vial rather than a prefilled syringe). However, the tradeoff for inefficiency is that this strategy may have less impact on quality, safety, compliance, or the manufacturer's ability to consistently and reproducibly produce the commercial product.
- Limiting the initial number of launch markets (e.g., launch only in the United States and European Union). This approach will facilitate introduction of the preferred product, processes, controls, and so on, via postapproval changes, before submission in the remaining markets. In this manner, the approach should reduce the resource burden in CMC and regulatory affairs by limiting the process version management as postapproval changes are implemented, and may provide optimum value to the company.

Considerations when selecting the launch site include facility fitness in terms of its technical capability, position in the supply chain to support launch markets, compliance and pharmaceutical quality system status, and resource levels. Additionally, the impact of the change from a clinical site to a commercial site must be analyzed. Issues related to this transition include:

- Technical requirements such as comparability/bioequivalence (BE) studies, stability studies, and process validation approach
- Regulatory hurdles
- Change management
- Need for technical support

The team should also compare the options to scale-up a process by building more capacity at the same scale and make the appropriate decision.

CONTROL STRATEGY

Control strategy is defined in ICH Q10 as follows [1]:

> *A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.*

For accelerated programs, the compressed timeline challenges the sponsor to develop the appropriate degree of process and product understanding, and to manufacture many batches of both clinical- and production-representative lots commensurate with normal expectations of regulatory authorities. Hence, it is highly desirable to agree with regulatory authorities—based on risk assessment and risk control—on what control strategy could be achievable to meet patient-acceptable standards. These agreements between the sponsor and authorities are highly individualized according to the science of the specific program, as well as the sponsor's amount of prior knowledge and understanding of the product and production processes. Where possible, there is significant benefit in leveraging prior knowledge.

Process Control Strategy and Associated Specifications

When proposing or developing a process control strategy with associated specifications, platform processes should be used as much as possible. Their use should support process development, product- and process-specific understanding, and the proposed process validation strategy. ICH guidelines should be followed as closely as possible because deviation leads to complexity, offsetting the benefit of using platform technology.

Sponsors need different approaches to set acceptance criteria for large molecule vs. small molecule products. Small molecule acceptance criteria are based on ICH Q6A [2] and ICH Q3 series [3] guidelines for impurities, plus ICH M7 [4] for assessment and control of DNA-reactive (mutagenic) impurities and ICH S9 [5] for anticancer pharmaceuticals. Large molecules specifications are set using ICH Q6B [6].

For accelerated programs, it is challenging to set the specification because manufacturing and clinical experience are limited. Bercu and colleagues have published useful considerations for setting specifications for impurities [7]. They propose approaches that may be used for specification setting based on clinical relevance in the drug development, registration, and postapproval phases of a product life cycle.

To focus the prioritization of process characterization/validation experiments, it is helpful to establish early a control strategy summary linking the quality target product profile, CQAs, presumptive CPPs, and the raw material control strategy. Early identification of CQAs and development of suitable analytical methods

for process performance qualification (PPQ) and pivotal trials could help mitigate the risk of relatively few lots and assist in discussions with regulators. The evolution of the control strategy—justified by a combination of process development data, knowledge of platform process performance, and incorporation of risk assessment and proposed risk control output—will aid in the negotiation of the "must have" components at the time of file vs. those that can be completed in parallel to PPQ or even postapproval.

When a sponsor is relying on less-traditional validation approaches for a biological/biotechnological product, early investment in an applicable cell-based potency assay alongside more platform-based methods will bolster confidence in the process robustness. In other words, having the right methods in place with the justified acceptance criteria will help strengthen the rationale that process monitoring will be sufficiently reliable to overcome any perceived risks associated with less-traditional validation approaches or a less-comprehensive validation data package filed in the initial biologics license application (BLA) or marketing authorization application (MAA).

For accelerated development programs, the process control strategy will almost certainly be developed based on limited product-specific manufacturing experience and may need to include a postmarketing commitment to reevaluate and adjust specifications after a specified number of commercial lots. For example, the process control strategy could include:

- Tentative specifications (i.e., acceptance criteria and, perhaps, analytical methods) for release, stability, and in-process controls at the time of MAA submission that could be optimized postapproval.
- Filing of preliminary CQAs and/or CPPs that could be updated postapproval, as per agreements with health authorities.
- Filing with monitoring tests or an increased sampling plan and subsequently "sunsetting" some testing or reducing the sampling when more data become available to support a decrease in testing. For example, some attributes such as residual host cellular DNA and host cell proteins (HCPs) may be removed from the specification if sufficient data confirm the process is effective in removing these impurities.

Analytical Method Readiness

Sponsors should take a risk-based approach to determine the extent of method validation to be done prior to the initiation of the qualification campaign. Depending on the intended use and risks associated with a method (e.g., compendial methods, general methods such as pH or osmolality, or platform analytic methods where significant knowledge and experience exists), complete validation may not be necessary. Instead, it may be sufficient to demonstrate by other means the suitability of a method to achieve the intended purpose. However, suitability should be completed before qualification campaign testing begins. Using platform analytical methods and processes as much as possible should minimize risk and will assist with validation approaches, such as phasing of analytical validation, and justifications to regulatory authorities.

Sponsors should take a risk-based approach to determine the extent of method validation to be done prior to the initiation of the qualification campaign.

Methods associated with product CQAs or product safety (e.g., assay testing for contamination) should be validated, with issues being resolved concurrent with the qualification campaign. The risks associated with the level of method suitability assessment and/or validation should be linked to an evaluation of process understanding and the acceptability of the stability strategy and stability data package. Risks associated with limited manufacturing and method experience may require more frequent sampling and enhanced assay system suitability criteria. In all instances, method validation reports must be approved and appropriate retesting or method bridging studies completed prior to PAI and release of the product for commercial distribution.

During development for an accelerated program, sponsors must pay attention to the strategy to bridge early assays to potentially different commercial analytical methods; it is important to retain enough samples from early batches. Sponsors should also consider the potential impact of this strategy on specification, total analytical control strategy, and testing laboratory operations. For biologics, the common assay changes are potency assay and HCP assay. Although the platform assay (i.e., enzyme-linked immunosorbent assay [ELISA]), may be sufficient as a potency substitute for early-phase development, authorities require that a potency assay reflecting the mechanism of action be in place at the time of registration. Developing the appropriate potency assay early to generate enough stability data is key for a successful filing of accelerated programs.

For an expedited program for a biologic substance, the reference material strategy should be designed early and cover the lifetime of the product. The primary reference material is expected to be representative of the pivotal clinical study material to ensure that the commercial batches also represent pivotal clinical study material. For an accelerated program, however, the pivotal batch could be an early clinical batch, which may not have been made at a scale sufficient to provide clinical process characterization or enough reference material for long-term use.

The reference material should be sufficiently stable, and a strategy must be developed to monitor drift. The strategy to designate a lot as primary reference material should have qualification/requalification protocols in place, with criteria to evaluate the following:

- Storage and manufacturing requirements
- Stability to monitor the trend
- Maintenance of supply continuity in both quality and quantity
- Linkage of lots to maintain representation of reference material used in pivotal clinical studies
- Any changes to the analytical methods (changes in methods, especially for potency reference material, may require bridging studies)

Ideally, the primary reference material would be the same material throughout the development and life cycle of a product. Secondary reference material should preferably be prepared and used for routine analytical testing soon after a primary reference standard has been established.

Stability Data and Shelf Life

For some accelerated programs, the shortened development time and limited availability of materials may make it impossible to generate sufficient stability data to comply with ICH requirements at the time of submission. A practical shelf life must be requested. For accelerated development products, the long-term (real-time) stability data available from an appropriate scale may be limited. Therefore, it may be necessary to file with reduced long-term stability data on the commercial process (launch material) and/or clinical scale batches. Discussions with health authorities may be required to reach a consensus on the amount of real-time stability data from representative batches to be included in the filing before the submission and the likely shelf life granted at time of approval. The following stability approaches can be considered:

- Leverage use of stability data from representative pilot-scale lots.
- Add clinical batches to the stability program for supportive shelf-life data.
- Use forced degradation and accelerated/stress stability studies to model the stability profile; enhance understanding; support comparability studies of clinical, supportive, and commercial material; and predict shelf life.
- Provide periodic stability updates to the health authorities.

Experience indicates that the shelf life granted by regulatory authorities varies depending on the amount of supporting data from clinical batches, expectations of specific reviewers, types of molecules, the medicine's risks and benefits, and other factors. This likely variation for a drug product only adds complexity to management of the supply chain postapproval.

Raw Materials

For drug substance synthesis for small molecules, it is extremely important that internal stakeholders, regulators, and, if necessary, third-party suppliers agree on the choice of starting materials (SMs) in a synthetic sequence as soon as possible. This agreement clarifies the GMP requirements, including the validation strategy. For guidance for SM selection, refer to ICH Q11, Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) [8], as well as the ICH Q11 Q&A [9], which offers additional clarification. However, there may be insufficient time to complete all desired studies identified in that guidance.

Tighter timelines may lead to a more conservative approach to identifying SMs, in which SMs are designated further upstream than may be proposed using the ICH Q11 Q&A. This approach could introduce additional costs and controls in the process that may not be necessary. While mitigation strategies may be implemented (e.g., manufacturing the final steps in the SM manufacture under GMP conditions) in case health authorities do not agree with the identified SMs, launch supplies may still be jeopardized.

Accelerated development may limit the time to evaluate and/or qualify multiple suppliers of raw material or intermediates. Being single-sourced for key intermediates may impact assurance of supply.

PROCESS VALIDATION

For products with accelerated development timelines, time or materials may be insufficient to complete all traditional process validation studies (i.e., hold-time studies, mixing studies, process ranges, worst-case linkages) and batch manufacture before submission. For small molecules, it is not necessary in all cases to complete validation by the time of the new drug application (NDA) submission; however, for large molecules (and "nonstandard" products in the EU), satisfactory completion of at least three full-scale batches at the intended site of manufacture of both drug substance and drug product is currently required. Because accelerated development programs may not allow completion of these large-scale studies before submission, alternate phasing strategies have been employed. Given that process validation itself should take a life-cycle approach as discussed, for example, in FDA Process Validation guidance [10], a holistic life-cycle approach could be proposed. In this approach, data from stage 1 (process design) and similar processes could be leveraged to reduce initial stage 2 (process qualification) requirements. This is further supported by a robust stage 3 (continued process verification) monitoring plan, which provides added assurance of the quality of each batch.

A risk-based approach should be taken to determine the process validation strategy to be used before the qualification campaign begins (i.e., the extent of process design/development data to collect from stage 1). Process validation associated with patient safety must be complete (e.g., sterility, viral clearance, microbial control) at the time of launch to patients. Potential justifications to support a flexible process validation strategy include the following:

- Acceptance of a smaller scale of production
- Concurrent release of product
- Modeling and "scale-down" process design to study factors that impact CQAs and CPPs

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If process validation is on the critical path to launch, some experiments can be viewed as more critical than others to process control strategy understanding. For example, for a given product's proven acceptable range series of experiments (and, therefore, reliance on appropriate small-scale models where applicable), it may be more critical to demonstrate that the process will reliably deliver a drug substance or drug product meeting the predetermined acceptance criteria and less critical to conduct column lifetime studies, which could be proposed as part of concurrent process validation or as part of the continued process verification protocol.

PHARMACEUTICAL QUALITY SYSTEM READINESS

An update and/or amendment to the PQS may be necessary because accelerated programs may not have historically expected data to readily support transfer of a process into a mature manufacturing PQS at a facility. Challenges are often experienced by development teams while navigating numerous development PQS requirements in a shorter than customary time frame. Challenges may also arise in the form of differing expectations between development and operations quality organizations. Such challenges are not unique to accelerated programs, but they do pose significant risk to the project's success given the aggressive timelines. For example, the use of a clinical manufacturing site for launch (which is unusual in a "conventional" development) may require a PQS upgrade to meet the standards of quality (i.e., documentation practices, deviation/change management) expected of a traditional commercial launch facility. In such cases, depending on the prior history of the facility, early engagement between the launch site and relevant operations' compliance teams may be necessary to ensure that the facility is positioned for successful execution of validation batches and prepared for inspection by health authorities.

There may also be differing interpretations of PQS requirements between local and global functions or between the company and contract manufacturing organizations. If such differences are not identified early in the process, they can result in rework or other project delays. It is important for the transfer team, launch site, and downstream parts of the supply chain (e.g., commercial filling) to communicate early and achieve alignment on standards for quality and compliance.

Forward planning of activities to manage PQS readiness is extremely helpful because the chosen launch site may not be familiar with the compromise between agility and formality required to support the early phases of launch from an accelerated development program. An operations site may be accustomed to more robust processes and having more data to support changes or deviations. Alternatively, a clinical site may not be familiar with the formality of PQS requirements for procedures in normal operations. Whichever site is chosen, considerable amounts of technical change management postlaunch are likely. Some factors to evaluate the level of agility and formality of the PQS are as follows:

- The PQS's ability to handle change management with agility. Careful planning and design of a proactive change management plan is a requirement for many accelerated development programs to address, for example, prospectively designed process changes. These proposed changes require a mature and potentially flexible change management system as a key element of the PQS.
- The appropriateness of standard operating procedures.
- The appropriateness of the levels and types of documentation.
- Staffing levels; for example, staff could be needed to handle the increased volume of investigations, which may be more intensive than usual. Additionally, in-process sampling/process monitoring activities will likely require more resources than a standard process would.

Quality risk management should be applied to identify and document risks to the accelerated program as they relate to PQS standards and to ensure appropriate control measures are in place to mitigate any accepted risks. Such assessments can then be used to prioritize activities and resources.

REGULATORY CONSIDERATIONS

Early, effective, and detailed communication between sponsors and regulatory authorities throughout development facilitates better and more informed CMC development decisions, which could lead to greater regulatory flexibility built upon a shared understanding of the risk-to-benefit profile. These discussions are particularly important when considering and developing a life-cycle approach.

When a life-cycle approach for a large molecule program is developed, it is most likely that use of comparability protocols and postapproval change management protocols (PACMPs) will be considered and proposed. Similar approaches should be considered for small molecule programs.

Some sponsors may find it useful to have discussions with authorities to reach consensus about the use of a product life-cycle management (PLCM) document as proposed in ICH Q12, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, Step 2 [11]. The PLCM document outlines the specific plan for PLCM that is proposed by the sponsor.

Considerations for submission include dossier content and global filing strategies.

Dossier Content

Dossiers should be written concisely and clearly to facilitate review, and they should include well-structured and well-presented justifications to support the proposed positions and rationales. For example, the dossier should have justifications for the use of supporting data and platform technology, as well as brief explanations of the rationale for referring to prior knowledge. The CMC story, which may not be complete, should be logically organized and well written. Proposed future studies, the rationale for prioritization, and how results would be communicated to reviewers should also be clearly presented. For example, the use of regulatory processes such as comparability protocols and PACMPs should be clearly explained

and include references to any regulatory agreements. If a traditional approach to a control strategy has been taken, it may be beneficial to explain why this approach has been chosen.

Global Filing Strategies

Global regulatory filing strategies are complex and often not driven by CMC considerations. Issues such as the amounts and types of clinical data, as well as the enthusiasm of a regulatory authority for the drug product and its impact on disease in a regulator's country/region, will have an impact. Given that an accelerated development program will be targeted to at least one of the ICH regions, the sponsor is likely to focus, at least initially, on meeting the requirements of that region.

Furthermore, given the strong possibility that the CMC program will be phased with a life-cycle strategy, filings in regions beyond those proposed initially will depend on many factors. For example, the timing of applications could be affected by supplements and variations filed in the initial regions as well as by the amount of CMC data and information available from the still-evolving CMC program.

CASE STUDIES

The following case studies illustrate approaches that teams have taken to overcome their particular challenges related to the key considerations and themes noted in this series of articles. Notably, in every case study, teams observed that accelerated development programs run more smoothly when they have processes in place to ensure support by internal stakeholders. Furthermore, most, if not all, programs reported that they encountered significant regulatory challenges due to the lack of global regulatory harmonization particularly with (but not limited to) postapproval submissions. This issue is extremely important for accelerated development programs because, in almost all cases, a life-cycle approach is employed in such programs.

Case Study 1—Large Molecule

In case study 1, the sponsor had many postapproval commitments from various markets. Challenges included:

- Qualification of tests for certain in-process sample types
- Completion of drug substance and drug product container-closure leachable studies
- In-process hold-time revalidation
- Reevaluation of acceptance criteria after a certain number of lots (lot release, stability)
- Low endotoxin recovery remediation
- More detailed risk assessments
- Stability data

To resolve these issues, the sponsor had to conduct the necessary work and carefully coordinate postapproval supplements for:

- Change to an improved method: Supplements were needed for approximately nine markets; in the other markets, the original MAA was filed together with the supplements.
- Addition of a new site: Supplements were filed for around 20 markets.
- Method transfers and optimized testing strategy: Supplements were filed for most markets.
- Shelf-life updates.

The team used the life-cycle approach, deferring some CMC studies as postapproval commitments, with the regulatory authority agreeing to this strategy in advance, and articulating the risks and benefits of a selected approach. The sponsor also needed to consider supply chain options to add a new site of manufacture postapproval to maintain supplies to patients. Inevitably, shelf-life updates were required. Additionally, technical challenges were associated with the setting of acceptance criteria and the need to remediate low endotoxin recovery. In this case, a strategy to minimize process changes was employed to facilitate initial submission, approval, and supply to patients.

Case Study 2—Large Molecule

In case study 2, the sponsor pursued an accelerated submission process for a BLA for a new drug product with Breakthrough Therapy Designation (BTD). Key issues included the low commercial volume anticipated and the challenge of having different drug

product clinical and commercial manufacturing sites in the scope. Issues related to the latter challenge included:

- All clinical/stability experience to date would be from the clinical site.
- Shelf-life claims would depend on the bridge from clinical to commercial manufacturing (ensuring process comparability).
- Sufficient shelf life would be needed to effectively commercialize/distribute product.

Key facets of the life-cycle strategy used to address these challenges were to:

- Submit the BLA without a drug product PPQ at the commercial site and with limited or no commercial site experience (i.e., clinical or stability batches).
- Leverage a validation life-cycle strategy that relied heavily on prior knowledge from similar products manufactured in the same facility on the same manufacturing line. This strategy involved:
  - One PPQ batch to be provided at initial submission or during the review cycle
  - Two more PPQ batches to be performed/provided postapproval as clinical/commercial demand dictated the need for supply
  - Regulatory alignment pending

This team proposed to use a life-cycle approach to submit a BLA without a drug product PPQ from the commercial site and with limited experience of commercial site manufacture. The process validation and site selection strategies are heavily reliant on leveraging prior knowledge and platform processes. In both cases, risks and benefits were identified. In this case, a minimizing process changes strategy was also employed to facilitate initial submission, approval, and supply to patients.

Case Study 3—Large Molecule

In this case study, the sponsor also pursued an accelerated submission process for a BLA for a new drug product with BTD. Notable challenges included nontraditional comparability, the supply strategy, stability data, assay validation and utilization, and the reference standard.

To meet these challenges, the sponsor met with the FDA every 2 to 3 months to ensure alignment between the submission and regulatory expectations. Preapproval within a span of 1 year and the following interactions and content occurred:

- Type B: The sponsor sought FDA concurrence with the sponsor's proposed CMC strategy and proposed package for comparability.
- Type B: The sponsor provided an overview of its supply strategy.
- Type A: The sponsor and the FDA discussed the comparability strategy and data for Material B and Material B'; the use of B' in confirmatory trials; and the filing of B' as commercial material.
- Type C: The sponsor shared challenges in development, such as the potency assay, PPQ, HCP assay, and reference standards strategy, and gained the FDA's concurrence on strategy prior to finalizing the BLA.
- Pre-BLA meeting: The sponsor and the FDA discussed the CMC-specific content and format of the planned BLA submission, including the retrospective review of PPQ data, the updating of stability data, and the data's ability to support extension of shelf life.

Furthermore, at the postapproval (Type C) meeting, the sponsor sought the FDA's feedback on the control strategy and the agency's concurrence on the filing strategy for the proposed analytical method and specification changes.

This case study highlights the importance of communication between sponsors and authorities for many CMC issues, such as:

- Supply chain options
- PPQ strategy
- Provision of stability data and agreement about shelf life

All of the sponsor's justifications leveraged prior knowledge, and platform processes, identified risks and benefits, and the strategy obviously used a life-cycle approach. In this case, a strategy to minimize process changes was also employed to facilitate the initial submission, approval, and supply to patients.

Case Study 4—Small Molecule

Case study 4 involved a small molecule NDA submission after phase 2 clinical data. Submission after phase 2 clinical data was potentially 6 years shorter than a "typical" program based on historical experience.

Major challenges were:

- The solid-state drug substance form needed to be changed after phase 1 dose-finding studies so it would have a form that was compatible with proposed clinical and commercial tablet manufacturing processes and to ensure suitable long-term stability in global markets.
- The early drug substance synthetic route was not amenable to the scale of manufacture necessary to support rapidly enrolling clinical studies.
- Phase 2 tablet clinical formulation was an enabled tablet suitable for rapid entry to clinic, but it was not considered the image or strength necessary for commercial markets.

To address these challenges, the sponsor used the following strategy:

- A broad screen of solid-state forms was performed, supported by predictive tools and tabletability studies. Once narrowed to two options, a relative bioavailability study was conducted between the original phase 1 form and the proposed commercial form. Once relative bioavailabiity was shown, phase 2 pivotal clinical studies were started using the phase 2 clinical formulation and this selected commercial form.
- Synthetic route and manufacture, from 10 kg to 300 kg scale, were optimized to support commercial tablet development, drug substance ICH stability studies, and manufacture of commercial drug product stability and BE study materials.

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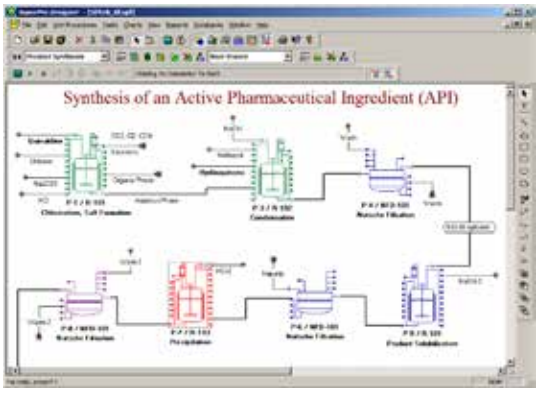

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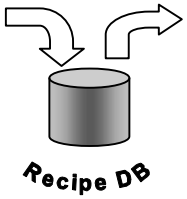

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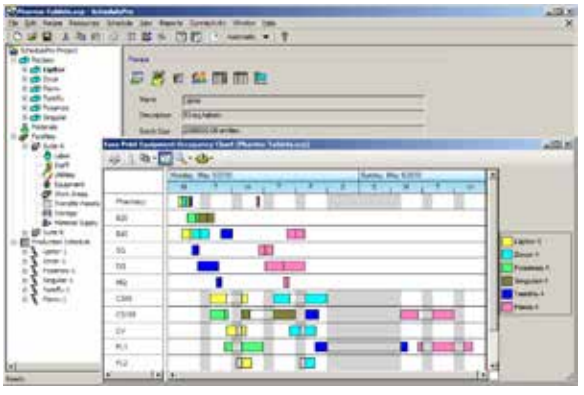

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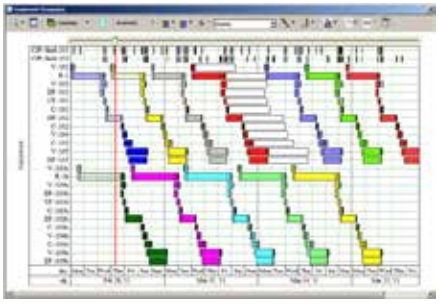

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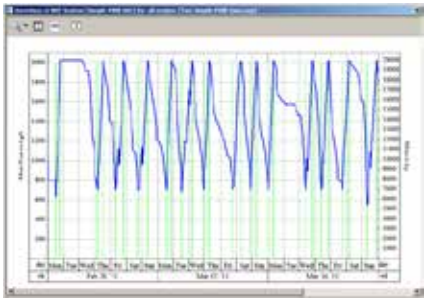

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- Commercial tablet formulation was developed in parallel with phase 2 clinical studies, evaluating formulation variants using predictive biopharmaceutical computational tools. A BE study was conducted to confirm the proposed commercial formulation is bioequivalent to the pivotal clinical study clinical formulation. This study was reported immediately before NDA submission. The commercial formulation was used in phase 3 confirmatory studies.

This case study had substantial risks beyond those expected in a conventional development:

- If another, more suitable (e.g., more stable), form were to be found later in development, the sponsor would have needed to redo the ICH stability studies and conduct another BE study. These additional studies would have involved significant delay and increased costs. Switching quickly and early from the phase 1 early drug substance form to the intended commercial form allowed for early commitment of the preferred drug substance form to clinical supplies for pivotal studies and to inclusion in the commercial tablet/ICH stability program.
- The impurity profile of the new drug substance synthetic route could not be qualified in time for NDA submission. If any new impurities were found in the optimized drug substance route, and the route were not qualified by virtue of their presence at some level in previous batches, the sponsor would have needed a toxicological qualification study (or studies) to qualify that impurity.
- The proposed commercial tablet formulation was not bioequivalent to the phase 2 clinical formulation. This could lead to a delay in launch supply and the need for an additional BE study of an alternate commercial formulation. Additional stability studies and process validation would be required for the alternate commercial formulation, resulting in a significant delay, added costs, and a risk to launch. Validation of clinical manufacturing facilities and process may have to be considered as a further mitigation step.

In this case, the company was able to deploy a skilled and knowledgeable workforce to understand the level of potential risk. With substantial resource commitment in terms of people and computational support, the sponsor managed to mitigate the highest risks successfully. This strategy was fully supported by internal stakeholders.

Interestingly, the total resources used for this 4-year (from first time in patients to filing) development program were comparable to the resources used for a typical 7-year program. In other words, the area under the curve is the same, but the peak of the accelerated program is higher over a shorter period of time.

Computational modeling, simulation, and predictions were used in all aspects of this program to minimize the risk associated with key decisions (form selection, drug substance synthesis scale-up, commercial tablet design, and prediction of BE performance). The program had no development "white space" (the time typically used to await a clinical decision point), which is used to to perform drug substance and/or drug product development activities and minimize risk. As a result, key development investments were made in parallel and at much greater risk than a "typical" program. These investments included the purchase of raw materials for the commercial drug substance route with commitment to a clinical supply with the selected commercial solid-state form of the drug substance for the pivotal study, the investment in ICH stability of the selected drug substance route before phase 1 ended, and the use of accelerated stability to predict long-term outcomes.

Case Study 5—Small Molecule

In this case study of drug substance synthesis, key challenges included:

- Supplier selection with respect to SM justification
- Purification strategy with respect to timing of route design and manufacturing route identification
- GMP strategy with respect to which steps to conduct or not conduct under GMP

The sponsor's strategy focused on the following:

- A commitment to purchase the SM before the control strategy was finalized and before data were generated (as recommended in ICH Q11 to select and justify a SM).
- The fairly aggressive choice for SM, which was considered risky for certain regional health authorities. SM selection should be determined by the technology required to manufacture intermediates.
- Use of an additional purification step (included in the common technical document) due to the conservative approach based on the tight timeline.
- The final few steps of SM being manufactured under GMP at vendors to mitigate risk.
- Inclusion of extra steps in the validation strategy (leveraging ICHQ7 Q&A for validation).

This case study exemplifies a strategy for selecting SM. In this case, an appropriate degree of process and product understanding was used to assess the risks and benefits of various approaches, and the sponsor took extra risk mitigation steps to minimize the harm to the project if a regulatory authority did not agree with the choice of SM. This approach, which required additional work compared to other strategies, had to be supported by internal stakeholders.

Case Study 6—Small Molecule

Case study 6 also involved drug substance synthesis. Three notable challenges were the development timeline (the sponsor sought to reduce it by 30% to 50%), the purification strategy, and optimization.

To address the acceleration of the development timeline, the sponsor used the following strategies:

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- Choosing the commercial route with limited demonstration of processes at scale and limited time to investigate all multivariable effects, which is higher risk.
- Delaying process improvements during commercial route development.
- Compressing DOE studies, forcing a segmented study of process.
- Executing pivotal clinical studies before full analytical development was completed.

The purification strategy involved:
- Using a less-robust, higher-risk process due to time constraints.
- Manually stopping (cooling) the reaction when complete. This was necessary because overreaction leads to difficult-to-remove impurities.
- Submitting a comparability protocol for the development of control strategy for the catalyst.

Finally, the optimization strategies included:
- Delaying the pursuit of robust catalyst for reaction. The current catalyst ligand is very water sensitive.
- Placing multiple materials, representative API for drug product manufacturing, on stability due to a solvent switch in the middle of the API campaign.
- Choosing to not reduce the stoichiometry of reaction material to nearly 1 equivalents.
- Utilizing extra resources to develop the commercial route while managing clinical supplies (the route to be abandoned), and to challenge the impurity qualification utilizing dual campaigns.

In this case, the risks and benefits for the choice of the drug substance synthetic route were used to select what studies to perform to develop an appropriate degree of process understanding and to defer some obvious potential process improvements (e.g., choice of catalyst). Risks and benefits were evaluated by building redundancy into the program (e.g., multiple drug substance stability programs), with the approaches (e.g., investment of additional resources) supported by the internal stakeholders. A life-cycle approach was used to develop a control strategy for the catalyst through communication between sponsors and authorities.

Case Study 7—Small Molecule

In this case study of a drug substance solid-state form, the notable challenge involved selecting the ideal solid-state form for commercial manufacturing of the drug product. The sponsor's strategy was:
- Choosing the solid-state form while knowledge of the polymorph landscape was limited.
- Performing additional work to ensure that the chosen form would be obtained after a lower-energy form was discovered.
- Accepting that scale-up of API crystallization would be a high-risk endeavor due to incomplete process knowledge.

In this case, analysis of risks and benefits led to the conclusion that sufficient process understanding had been developed to support the scale of the chosen, higher-energy polymorph solid-state form and that the lower-energy polymorph would not be encountered on scale-up. This strategy required support from internal stakeholders.

Case Study 8—Small Molecule

In this case study, a notable challenge involved the drug product development timeline. Strategies to support the accelerated timeline included the following:
- Using the same clinical formulation and dosage form for the initial commercial launch of the drug product.
- Condensing brainstorming regarding the commercial route to submission.
- Focusing efforts on process reliability over yield and cost of goods.
- Deferring process optimization to postapproval.
- Submitting limited stability data.
- Utilizing single-source vendors.

In this case study, the sponsor evaluated the risks and benefits of using a less-efficient drug product formulation with single-sourced vendors for initial submission, approval, and supply to patients. An appropriate degree of process and product understanding was developed to support submission and launch, with a life-cycle approach used to advance process optimization postapproval. Communication between the sponsor and authorities was essential to ensure they were in agreement regarding the supply of limited stability data.

Case Study 9—Small Molecule

This case study highlights process validation challenges related to analytical development and the use of few full-scale validation lots. The sponsor's strategy was to:
- Focus on high-priority test methods.
- Use partially validated methods for qualification lots.
- Complete validation before commercial release.
- Negotiate acceptance to use clinical API for drug product validation.
- Build upon process and product platform knowledge and justification.
- Leverage continued process verification principles.
- Utilize clinical batch process data to enable the concurrent validation approach.

The sponsor evaluated the risks and benefits on the analytical validation approach to allow focus on the high-priority methods. Communication between the sponsor and authorities, the leveraging of prior knowledge and platform processes, and a life-cycle approach were used to develop the process validation strategy, which used data from clinical drug substance lots supported by data supplied during the continued process verification phase and submitted postapproval.

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PATIENT-CENTRIC SPECIFICATION:

Regulatory and Industry Progress

By Daniel Y. Peng, Joel Bercu, Ann K. Subashi, and Lawrence X. Yu, PhD

On 5 June 2018, a plenary session entitled "Patient-Centric Specification" (PCS) was held at the 2018 ISPE Quality Manufacturing Conference in Arlington, Virginia. More than 160 professionals from worldwide innovator and generic pharmaceutical companies, academia, and regulatory agencies attended. The objective of the session was to discuss the recent regulatory and industry progress on this topic. Attendees discussed the opportunities, challenges, and future directions for establishing PCSs.

BACKGROUND

As defined in International Conference on Harmonization (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 [1].*

The fundamental intent of this definition is to ensure that a drug product will deliver the therapeutic benefit to the patient as stated in its labeling (the intended performance).

However, interpretations of this ICH guidance by different regulatory agencies have diverged during the last two decades. Historically, it has been usual and customary to set drug substance (DS) or drug product (DP) specifications based on the variability observed in a limited number of clinical batches without consideration of the actual impact of the variability on patient safety and product efficacy. This practice has the potential to cause significant and deleterious consequences when applied to product specifications.

These consequences may include:

- The unnecessary rejection of batches that would have met patients' needs (safe and effective medicine), which could, in turn, lead to drug shortages
- Unintentionally allowing manufacturers with poor manufacturing processes to broaden limits in their specifications
- Limiting manufacturing process to 2 to 3 sigma, thereby reducing the flexibility of manufacturing changes and increasing manufacturing costs

To address these issues, ISPE established a PCS technical team under the Pharmaceutical Quality Lifecyle Implementation (PQLI)® Committee in December 2016. Members of the team are volunteers from global pharmaceutical and biotech companies with expertise in toxicology; chemistry, manufacturing, and control (CMC) regulatory affairs; quality assurance; quality control; and DS/DP development and manufacturing.

Since its founding, the team has had monthly meetings to discuss the opportunities and benefits of PCS and share their experiences in developing PCS in the global regulatory landscape. The objective of the session at the ISPE Quality Manufacturing Conference was to share the current views of the PCS team on this topic, especially as it relates to DS/DP impurity specification limit setting. In addition, Lawrence X. Yu, Deputy Director of the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Office of Pharmaceutical Quality (OPQ) was invited to give the FDA's perspective on patient-focused quality standards. The following is a summary of the presentations and highlights from the panel discussion between the audience and the speakers.

PCS AND IMPURITY QUALIFICATION

Joel Bercu, Senior Director, Nonclinical Safety and Pathobiology, Gilead Sciences Inc., gave a presentation regarding the ISPE PCS team's views on PCSs for DS/DP impurity and impurity qualification using nonclinical approaches. He started the presentation by referring to the part of the ICH Q6A definition of specification stating that specifications "should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product." He went on to explain the relationship between PCSs and batch data. Ideally, PCSs would be set inside the range of the acceptable safety/efficacy boundaries. These limits should be based on knowledge of the product and its intended performance (safety and efficacy) in patients. However, this fundamental focus on safety and efficacy is unfortunately sometimes obscured by the notion that batch manufacturing history is paramount to the setting of specification criteria at the point of registration.

After this general introduction, Bercu focused on the setting of acceptance criteria for DS impurity and DP degradation products. He gave a high-level review regarding the source of impurities (DS process impurity and DS/DP degradation products), as well as the current ICH guidelines (i.e., ICH Q3A[R2], Q3B[R2], Q3C[R7], Q3D[R1], M7[R1], and S9) for the safety testing of impurities, residual solvents, heavy metals, and mutagenic impurities [2–7]. He pointed out the qualification threshold is phase dependent. Values are recommended by ICH Q3A(R2)/Q3B(R2) for chronic exposure, and a qualification threshold is recommended for early-phase clinical trials less than six months in duration for nonmutagenic impurities [8]. If the qualification threshold is exceeded, safety data are needed to justify the higher level of impurity. If an impurity is considered mutagenic, then a limit lower than the ICH Q3A(R2)/Q3B(R2) qualification threshold can be established using the threshold of toxicological concern (TTC) concept. If there is a sufficient amount of toxicology data for an impurity, a permitted daily exposure (PDE) or an acceptable intake can be developed based on the toxicity data.

However, Bercu explained, current practices for setting acceptance criteria rely heavily on process experience from a limited number of clinical batches using some statistical analysis (e.g., process capability, tolerance interval, or range from the minimum and maximum limits attained during development), rather than safety and toxicity qualification data. The "process experience–based" approach does not answer the question of whether the predicted variability will impact product safety and efficacy. In addition, it is unreliable without lengthy process experience. A minimum of 30 batches in a statistical control state may be necessary to provide a reliable forecast of variability of future manufacturing batches [9]. Last, lowering the impurity specification is not always the best solution, as it can impact other quality attributes, resulting in more environmental waste and increased manufacturing costs. Therefore, he recommended leveraging the safety data to ensure appropriate PCSs and cautioned against being overly restrictive with impurity specifications based on limited batch data.

> Ideally, patient-centric specifications (PCS) would be set inside the range of the acceptable safety/efficacy boundaries.

CASE STUDIES AND GLOBAL REGULATORY CHALLENGES

Ann K. Subashi, Senior Director, Global Regulatory Affairs CMC, Pfizer, Groton, Connecticut, shared three industry case studies on how to establish PCSs for DS/DP impurities and discussed some of the global challenges arising from divergences in ICH guideline interpretation and implementation in different regions.

The first case study represented the global registration experience for one inorganic impurity attribute, palladium (Pd), in a chemically synthesized drug substance (small molecule). A limit of not more than (NMT) 500 parts per million (ppm) for Pd in the drug substance was initially proposed and was supported by the EMA 2008 Guideline [10] and ICH Q3D [5], which allows for an 800-ppm limit based on the PDE for Pd. The initially proposed specification limit (NMT 500 ppm) was accepted by ICH Regions 2 and 3. However, ICH Region 1 requested a tighter specification (NMT 200 ppm). The Region 1 request was related to two concerns: First, Pd offers no therapeutic benefit to the patient; second, in some cases, higher doses may be used for other indications, or additive exposure may occur due to combination use with other drug products. Notably, at the time of the registration, there was no discussion or plan that higher doses would be marketed; therefore, the dose concern from the country seemed to be unfounded. Addressing the second concern related to co-dosing and the potential for an additive exposure to Pd was a challenge because it was difficult for the applicant to determine the levels of Pd in other drug products that were not within its own portfolio. Furthermore, the defined PDEs already take into account the potential for exposure from multiple sources, so a safety factor is built into the PDEs. In this case, the company was forced to control the impurity to the lowest levels possible. A palladium scavenger step was developed, validated, and introduced postapproval to meet the Region 1 specification limit. The additional measure of control cost the research-and-development organization many months of development time, increased the overall cost of the commercial process, and added time to produce each batch of the active pharmaceutical ingredient.

The second case study was for an impurity that is also a significant metabolite in the DP specification. The manufacturer initially proposed an NMT 0.8% limit for this metabolite based on product clinical absorption, distribution, metabolism, and

excretion (ADME) and nonclinical toxicology data. This limit was accepted by ICH Regions 1 and 2. However, ICH Region 3 requested a tighter specification limit based on actual batch data. The applicant in turn used a safety-based argument showing that the in vivo level of this impurity was higher than the level in the proposed specification. However, the regulatory health authority insisted that the specification should be based on batch data and the mean plus 3 standard deviations, rather than accepting the justification based on holistic knowledge of the product and toxicology qualification data. After numerous rounds of communications, the applicant and the health authority compromised, establishing a final specification limit (NMT 0.4%) that fell between the originally proposed specification and the batch data results.

The third case study concerned unconjugated payload in an antibody drug conjugate (ADC) product comprising a monoclonal antibody (IgG4) conjugated via lysine chemistry to a calicheamicin derivative. Nonclinical toxicology data evaluating the conjugate and unconjugated payload provided evidence that the toxicity profile of the ADC principally related to nonspecific binding of the conjugate rather than from the unconjugated payload. A limit (NMT 4.0%) for the unconjugated payload in drug product was initially proposed and equated to a safety margin greater than an order of magnitude (1/25) from the no observed adverse effect level (NOAEL) for the unconjugated payload. Region 4 approved the acceptance criteria based on the safety margin. However, Region 2 approved a limit of NMT 2.0% based on the maximum value observed in the clinical batches, and Regions 1, 3, 5, and 6 approved a specification limit of NMT 3.1% based on a tolerance interval calculation using data from the eight clinical batches.

These three case studies clearly illustrate divergence among the different health authorities regarding the appropriate basis for establishing the acceptance criteria for DS/DP impurities. There is no evidence that the differences in quality standards actually bring any value to patients or improve product safety. However, it is certain that varied quality standards for a product increase the complexity in pharmaceutical quality systems as well as supply and distribution plans. This increased complexity in turn leads to increased costs and the potential for issues with supply continuity.

PATIENT-FOCUSED QUALITY STANDARD

Yu gave a presentation on the FDA's perspective regarding patient-focused quality standards. He stated that a product is of high quality if it is capable of reproducibly delivering the therapeutic benefit to the consumer as stated in the label, is free of defects, and presents no undeclared risks. A patient-focused quality standard is a criterion to which a drug product should conform to deliver the intended therapeutic benefit. Establishing such standards can help not only reject batches with poor quality but also increase flexibility in pharmaceutical manufacturing by preventing too high a reliance on process capability to establish quality standards. Patient-focused quality standards support the FDA's vision of "a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drugs without extensive regulatory oversight" [11].

Quality standards under the quality-by-testing paradigm are established based on data from one or more batches. When testing must be done to release batches, acceptance criteria could be overly sensitive, unnecessarily rejecting batches that would have met patients' needs, or acceptance criteria could be insufficiently sensitive, rewarding manufacturers with poor manufacturing processes and controls. In contrast, under the quality-by-design paradigm, acceptance criteria are established based on patient impact. Yu noted that testing may not necessarily be needed to release batches [12], and acceptance criteria should be decoupled from process variability/capability.

Recently, the FDA issued a manual of policies and procedures (MAPP 5017.2) on establishing impurity acceptance criteria [13] and a dissolution guidance for immediate-release, solid-oral-dosage-form drug products containing highly soluble drug substances [14]. The impurity MAPP provides information about establishing impurity acceptance criteria. It documents the CDER practice of focusing on the needs of patients rather than the manufacturing process in evaluating impurity specifications. The dissolution guidance establishes standard dissolution methodology and acceptance criteria that are appropriate for highly soluble drug substances that are formulated in immediate-release dosage forms. The guidance recommends that the drug product dissolution acceptance criterion be based on the high solubility of the drug substance, with a recommended single-point dissolution specification of 80% in 30 minutes—rather than an unnecessary multiple-points dissolution specification—for an immediate-release solid oral dosage form containing a high-solubility drug substance as defined per the Biopharmaceutics Classification System (BCS). Both the FDA impurity MAPP and dissolution guidance move the FDA to the direction of patient-focused quality standards.

Yu also pointed out that, moving forward, the FDA will encourage the development of patient-focused dissolution standards for extended-release dosage forms. It is hoped that future in vitro dissolution testing for an extended-release dosage form would be more predictive of the dosage form's in vivo performance. The impact of critical material attributes and critical process parameters on in vivo performance could then be quantitatively assessed by in vitro dissolution. This will provide scientific and risk-based knowledge to support patient-focused quality standards to ensure high-quality drug products that maintain safety and efficacy throughout the product life cycle.

PANEL DISCUSSION

Question 1 (asked by Yu): Can industry collect more case studies to show the global regulatory divergence that industry is facing?

Daniel Y. Peng, Director in Global Regulatory Affairs CMC Biologics at Merck, responded: Yes, the ISPE PCS team is working with member companies to collect more case studies to holistically understand the magnitude of the global divergence of specifications setting.

Subashi elaborated regarding the challenges that pharmaceutical companies are facing regarding global submissions and commercial specification negotiations during application review. The negotiations for specification setting often happen independently for each market or region and typically occur while seeking initial market approval, when the pressure is on to get the product to market. At the end of the day, particularly for complex products, the applicant ends up with manufacturing based on the most restrictive criteria to ensure global supply. This means that just one market with a different view can severely impact manufacturing operations and significantly increase complexity in pharmaceutical quality systems and supply and distribution plans. This complexity could ultimately lead to increased costs and potential issues with supply continuity. It would be very helpful if industry and global regulators could talk more openly about the science behind the rationale as well as what the real risks are. Efforts toward more harmonization based on PCS criteria could bring significant value.

Question 2: (to Yu) Can you share with us the implementation status of the MAPP (5017.2)? Has there been anything that's happened with the reviewers in the Office of New Drug Products (ONDP) and the Office of Lifecycle Drug Products (OLDP), and have you seen any differences regarding what's being submitted in the application in terms of specification?

Yu responded: MAPP 5017.2 was developed by OPQ with representatives from all relevant OPQ suboffices, including ONDP, OLDP, Office of Biotechnology Products (OBP), and Office of Process and Facilities (OPF). It provides guiding principles and approaches for establishing DS and DP impurity acceptance criteria for nonmutagenic impurities in new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs), based on the consideration of clinical relevance (safety and efficacy). The initial effective date of this MAPP was 18 January 2018. Hence, this MAPP has been already implemented in and followed by the OPQ suboffices focused on application assessment. Of course, if there is any significant issue or inconsistent assessment practice uncovered by industry, the FDA welcomes the applicant to have open communication with the agency.

Yu also clearly emphasized that even though the FDA wants to decouple the setting of acceptance criteria from process capability, manufacturing process consistency should be monitored and maintained during the production of the DS and DP as part of the quality system.

He indicated that he has not seen any differences in terms of specification setting for different types of applications (ANDAs vs. NDAs). He asked Stephen Miller, Branch Chief, Division of New Drug Product I, ONDP/OPQ/CDER/FDA, to further comment on this question regarding the assessors' experience. Miller indicated that he was encouraged by the concept of MAPP 5017.2, which is in alignment with ICH Q3A/Q3B guidelines for impurities when there are established toxicology data, such as solvents or metals. When there are no toxicity data generated to support an impurity, the qualification thresholds as defined by ICH Q3A(R2) and Q3B(R2) are the standard and should be followed, and this consideration is included in the MAPP. This is also true for ICH M7, where the acceptable level of a mutagenic impurity is the TTC. Miller questioned whether there are any cell-based or computational assays that can be used to determine the toxicity of a degradation product vs. traditional animal studies.

Bercu responded that there is not a good cell-based or computational assay that can represent the multiorgan toxicity as observed and obtained in an in vivo study. There is conservatism built into the traditional animal study. The NOAEL derived for an impurity in a qualification study is not a true NOAEL but a fraction of the NOAEL for the DS. Therefore, how we calculate toxicology-based limits for degradation products is inherently conservative.

Miller commented that he did not mean to single out degradation products except to note that they may be difficult to assess given that they are close to the toxicology-based limit from an animal study. Bercu responded that it is important to spike degradation products in a toxicology qualification study to help demonstrate a higher margin for the toxicology limit and the specification.

Question 3: Once a company has generated the animal toxicity data, how do you translate/back-calculate the limits for human beings?

Bercu responded: The approach as specified by ICH Q3A is to make sure the absolute amount or dose in animals is not exceeded in humans. However, some health authorities have requested lowering the acceptable dose by an additional factor, which is not recommended by ICH Q3A.

Question 4: What can industry and the FDA do to gain more acceptance for patient-centric quality standards globally?

Subashi responded: FDA MAPP 5017.2 is setting a clear direction and guiding principles for FDA OPQ assessors in assessing DS and DP impurity limits in NDAs, ANDAs, and BLAs. Industry is pleased to see that the FDA is moving in this direction to accept acceptance criteria based on clinical relevance (safety and efficacy). The pharmaceutical industry needs to develop and share more case studies throughout the scientific domain to bring awareness to a wider audience, continue discussions between industry and multiple regulatory authorities in forums such as this plenary session, and pursue available efforts through joint reviews.

While the MAPP is helpful, influencing other guidelines is a priority for the future. While we may continue to see global divergence, we should be moving toward global convergence. Convergence of major ICH markets could go a long way in influencing the acceptance of PCSs globally.

Question 5: If the push is to manufacture to the most stringent criteria to achieve global supply but manage by exception, how are the exceptions documented in quality systems and inspection?

Subashi responded: We tend to avoid such situations. The palladium example is an excellent case for which we adjusted manufacturing process to meet the criteria. That said, it [the need for exceptions] can come up and ends up as a challenge in the quality and distribution systems to enable release to certain markets.

Question 6: Have you ever run into a situation where the manufacturing risk was so high when considering the regulator's suggested specification criteria that you needed to push back hard and it could have impacted product approval?

Subashi repsonded: Yes, we have.

She then used as an example the third case study (the unconjugated payload), where Region 2 consistently pushed the applicant to tighten acceptance criteria that reflected the minimum/maximum of clinical exposure for multiple attributes even after the applicant had presented their view on what was relevant to patients. Considering the relatively limited numbers of batches used in clinical studies for that program and applying the tighter acceptance criteria to multiple attributes could lead to an extremely high batch-failure rate, which would result in the product not being commercially viable.

In this case, the applicant evaluated the practical implications and process capability for each attribute. They ultimately decided they could live with the tighter acceptance criteria . This is because the applicant improved the defined commercial process and updated the analytical methods where they did not have a high risk for failure anymore, even if they accept the tighter criteria as the health authority requested. Irrespective of having a patient-centric argument reflecting the toxicology understanding around why higher levels of unconjugated payload would not present a safety risk, the applicant decided it wasn't worth continuing the debate when they had more significant issues to manage to gain approval and have a commercially viable product.

CONCLUSION

Highlights from the session are as follows:

- A paradigm shift is needed for both industry and health authorities. Establishing PCS can help not only reject batches with poor quality but also increase flexibility in pharmaceutical manufacturing by decoupling the setting of specification acceptance criteria based on drug product safety and efficacy (voice of patient) from process capability (voice of process).
- The ISPE team recommends leveraging the safety data to ensure the establishment of appropriate PCSs for DS/DP

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impurities. One should be cautious about being overly restrictive regarding impurity specifications based on limited batch data.

- There are limited examples of a PCS being successfully set. However, many efforts may be slowed by the significant divergences among the different health authorities regarding the basis for establishing appropriate acceptance criteria for DS/DP impurities. Varied quality standards for a product increase complexity in pharmaceutical quality systems, as well as supply and distribution plans. This complexity in turn can lead to increased costs and potential issues with supply continuity.
- The FDA Impurity MAPP (5017.2) and the recently published dissolution guidance clearly indicate that the FDA is moving in the direction of patient-focused quality standards.
- Continued discussions between industry and multiple regulatory authorities are needed. PCS could be an important cornerstone to achieve global harmonization.

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Disclaimer

This article contains an abridged, unofficial summary of an FDA regulator's responses during a presentation and panel dialogue at a conference that has not been vetted by the agency. The responses are an informal and brief synopsis of the speaker's views, and do not represent official guidance or policy of the FDA.

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Lawrence X. Yu, PhD, is the Deputy Director, Office of Pharmaceutical Quality, and Acting Director, Office of Process and Facilities, for the US Food and Drug Administration, where he oversees new, generic, and biotechnology product quality review and inspection. Lawrence created the question-based review, defined the pharmaceutical quality by design (QbD), inaugurated the FDA modern review system Integrated Quality Assessment (IQA), initiated the Emerging Technology Team (ETT) program, developed the FDA historic concept of operations agreement to integrate review and inspection, and originated the Knowledge-aided Assessment and Structured Applications (KASA) initiative. He originated the compartmental absorption and transit (CAT) model that laid the foundation for the commercial software GastroPLUSTM and Simcyp. He is a Fellow of the American Association of Pharmaceutical Scientists and an Associate Editor of the *AAPS Journal.* Lawrence has authored/coauthored over 150 papers and given over 300 invited presentations.

2019 ISPE ANNUAL MEETING & EXPO:

Modernize, Globalize, and Transform

By Susan Sandler

The 2019 ISPE Annual Meeting & Expo will be held 27–30 October in Las Vegas, Nevada. The theme is "Modernize. Globalize. Transform." Michael L. Rutherford, Program Committee Chair and Board Ambassador for ISPE, and Executive Director for Computer Systems Quality and Data Integrity at Syneos Health, provided a preview of highlights for conference attendees, including notable new features and his take on the meaning of this year's theme.

This year's Annual Meeting & Expo offers pharmaceutical professionals the opportunity to engage in industry-critical conversations. Attendees from all levels of the industry will include representatives of drug manufacturing, supply chain, devices and equipment and services, and global regulatory agencies. Rutherford shared insights about the importance of the opportunity for the industry to come together and the critical nature represented by this year's theme in his conversation with *Pharmaceutical Engineering*.

The theme of the 2019 ISPE Annual Meeting & Expo is "Modernize. Globalize. Transform." Why is this theme of such great importance right now? What knowledge will attendees take away related to this theme that will help them in their day-to-day work?

When we selected the theme for the 2019 Annual Meeting, we felt these three words truly reflected where the pharmaceutical industry is making a real difference to our stakeholders, and especially to patients. We are leveraging new and rapidly evolving technologies and capabilities to modernize and accelerate the development and manufacturing of advanced therapies. Advances in biotechnology, cell and gene therapy, continuous manufacturing, and Pharma 4.0 are really helping drive this modernization and transformation of our industry. And the global nature of our industry continues to influence and shape the future, with more complex global supply chains and increased regulatory implications. ISPE is helping transform our workforce of the future though our Women in Pharma® and Young Professionals initiatives, both of which have featured events at this Annual Meeting.


Michael L. Rutherford

The Annual Meeting is ISPE's largest event of the year, with more than 50 educational sessions, and many opportunities for attendees to interact with global industry and regulatory experts and opinion leaders. It's a chance to learn about the current industry, technology, and regulatory trends and best practices, so attendees can apply those learnings in their own companies. It's also a chance to interact with a wide variety of vendors in the Expo Hall, and build a network of industry contacts and colleagues.

The Annual Meeting brings together both new members and more seasoned industry experts. How can both new and expert industry members make the most of the opportunity to interact at the Annual Meeting?

The mix of new members and more seasoned industry experts is what makes the Annual Meeting, as well as other ISPE conferences,

so special. Where else can you get a cross section of more than 2,000 attendees together to interact, network, share, and learn?

But you only get out of it as much as you put into it: Take the initiative to interact with others. Don't be afraid to approach a speaker with a question or introduce yourself to another attendee, especially during networking events. It's been my experience that industry experts, regulators, and ISPE volunteers are more than happy to share their knowledge and experiences. As a "seasoned" member, I make a point of saying hello and chatting with attendees I have not met before, especially new members, students, Young Professionals, and first-time attendees. These members are the future of our industry. It's also important to talk with the vendors in the Expo Hall because they play a key role by helping support conference events and providing opportunities to learn about new developments in our industry.

I challenge every attendee, whether a new or seasoned member: Each day of the conference, say hello and introduce yourself to at least 10 attendees you have not met before. You'll be amazed how big an impact that will have on your overall attendee experience.

What are you looking forward to hearing about/learning more about at the Annual Meeting?

There are so many sessions and topics to choose from, so this is actually a difficult question for me. I always find the plenary sessions and keynote speakers interesting because they provide the senior leadership perspectives for our industry. This year is no exception because the keynote presenters represent a diverse group of companies and product sectors, including biotechnology, rare diseases, and a clinical research organization. These different perspectives should offer something new for everyone. As in past years, to remind ourselves why we are in this industry, we will continue our practice of including the patient perspective. These plenaries will definitely help emphasize our theme for the conference and set the stage for an amazing event the rest of the week.

With respect to a specific session or topic, I think everyone has their area of specialization that they trend toward. For me, it is information systems and the regulatory-related sessions, including the Regulatory Town Hall. But I also find the new technology and innovation topics to be very interesting. So let me provide some advice that everyone can use relative to attending the education sessions. First, download the ISPE Events App for the Annual Meeting on your phone or tablet. It provides the most up-to-date information about the sessions. Prior to the start of the meeting, identify and bookmark the sessions you are interested in; then they will appear in the app on My Schedule. This is your personalized schedule for the conference and will help you make sure you do not miss anything. It will also identify any conflicting sessions. If a conflict happens, leverage your new acquaintances and/or colleagues and friends to share notes on your respective sessions. You will also have access to the presentations after the meeting.

Finally, as the Program Chair this year, the one thing I really want is your feedback on the conference. Make sure you complete the survey after the Annual Meeting,because we do utilize the feedback to help improve the Annual Meeting next year.

What else do members need to know about the Annual Meeting?

I mentioned earlier that ISPE is helping transform our workforce of the future though our Women in Pharma® and Young Professionals initiatives. For the first time ever at the ISPE Annual Meeting & Expo, students and YPs will have a Hackathon, which offers the opportunity to compete to develop solutions to real-world problems while developing lasting connections. The success of the pharma industry's efforts to modernize, globalize, and transform to adapt to new challenges and innovations depends on knowledgeable, creative, and driven leaders at all levels. And the Annual Meeting provides a great opportunity to build those leaders.

The Hackathon format has been extremely popular at the last three ISPE Europe Annual Conferences and provides great networking and collaboration opportunities among students, YPs, industry, and ISPE staff and board members. We need to continue to encourage and support the development of our students and YPs. I challenge industry management, academic leaders, and ISPE members and groups to identify and sponsor a student or YP's participation in the first ISPE Annual Meeting Hackathon and attendance at the Conference this year. In addition, I encourage you to sign up and participate in the Women in Pharma® events at the conference, including the off-site Women in Pharma® event on Monday evening 28 October. These events will have a lasting and positive impact on individual careers and the future of our industry.

A final note: ISPE will be announcing a new three-year Strategic Plan at the Annual Meeting. Attendees will have the opportunity to learn firsthand about the Strategic Plan, which will continue to build on our work in the last few years with added focus on important future trends of the industry.

About the author

Susan Sandler is the Editorial Director of *Pharmaceutical Engineering*.

Get the latest information on the 2019 ISPE Annual Meeting & Expo program, registration, and more at:

https://ispe.org/conferences/2019-annual-meeting-expo

2019 ANNUAL MEETING & EXPO

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TRAINING | **31 OCTOBER–1 NOVEMBER**
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Vital Statistics

The four-day 2019 ISPE Annual Meeting & Expo features:

- **Six extensive education tracks** on industry-critical initiatives—focusing on excellence, modernization, and harmonization in pharmaceutical science and manufacturing
- **More than 85 hours of targeted technical sessions** from both industry and regulatory leaders
- **Over 200 exhibitors** featuring innovative technologies and services
- **ISPE Discovery Stage** showcasing cutting-edge modernization in pharma products and services in the Expo Hall
- **Two days** of in-depth classroom training courses on 31 October and 1 November
- **Over 24 hours of networking opportunities,** including:
  - More than 50 plenary and technical sessions
  - Facility of the Year (FOYA) Awards Program
  - Membership Awards Program
  - Facility tours
  - 5K charity run/walk
  - Interactive workshops
  - Young Professionals events
  - Women in Pharma® events

Educational Tracks

- Facilities and Equipment
- Information Systems
- Innovation in Pharmaceutical Engineering
- Process Development and Manufacturing
- Quality Systems & Regulatory
- Supply Chain Management

ISPE Foundation Student Travel Grant Recipients Speak Out

The ISPE Foundation awarded 14 Student Travel Grants to bring 14 students to the 2018 ISPE Annual Meeting & Expo. Investing in the next generation of pharmaceutical engineers is a goal of the Foundation, which was formed in 2018.

Two students received the Women in Pharma® Foundation Student Travel Grant. The other 12 students won their Chapter or Affiliate's International Student Poster Competition and received Travel Grants in recognition of that achievement. Each student received the cost of registration and a stipend of $500 for travel within the US or $1,000 for international travel.

TRAVEL GRANT RECIPIENTS

Recipients of the WIP Student Travel Grants

- Jordan Krist, University of Colorado Boulder
- Damilola Oluyemo, master's program enrollee, Rutgers University

International Student Poster Competition Winners

- Abed Abugherir, San Jose State University
- Marty Burns, Stevens Institute of Technology—PhD candidate and winner of the graduate International Student Poster Competition
- Kirivann Chhoeun, Massachusetts College of Pharmacy and Health Sciences
- Boonta Chutvirasakul, Mahidol University, Visiting Scholar at University of Kansas
- Mia Hall, North Carolina Central University
- Kinza Hussein, Massachusetts College of Pharmacy and Health Sciences
- Nick Lewis, University of California San Diego
- Cy Rodriguez, University of the Philippines—winner of the undergraduate International Student Poster Competition
- Nicole Rosselli, Rowan University
- Vishnu Sunil, National University of Singapore
- Lilley Tran, San Jose State University
- Melissa Wooten, North Carolina Central University

IN THEIR OWN WORDS

The WIP application required students to write about why they believed they should receive the grant to attend Annual Meeting; International Poster Competition participants wrote essays on what it means to them to be able to attend Annual Meeting.

The following are excerpts from attendees' essays about their experiences at the Annual Meeting in 2018. Their feedback demonstrates the tremendous value the Annual Meeting has for budding pharmaceutical engineers and the industry they are joining.

Abed Abugherir

The ISPE Annual Meeting & Expo was astounding! The event was so organized and informational, allowing attendees to learn and be enlightened with the different pharmaceutical topics available. Personally, I have gained a bright insight on what the industry is doing to improve the technology in drug production and delivery, as well as improving patients' lives by finding cures for rare diseases. The booths in the exhibit hall were amazing in terms of how friendly the people were as they explained their functions and goals.

In regard to the International Student Poster Competition, it was fantastic to learn about what other students are researching at both the undergraduate and graduate levels. Also, competing with them allows one to know that the research done is great because it is on an international level overall.

Marty Burns

I've had the opportunity to participate in many conferences, poster sessions, and networking events, but the 2018 ISPE Annual Meeting stands apart. The social, professional, and scientific presence at the meeting was key to making it so enjoyable. I was very impressed by the attention and access given to Young Professionals

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(YPs), both in the social events and in the technical material presented. ISPE organized many exciting events for us, including multiple networking sessions, a brewery tour, and a dinner party featuring many excellent restaurants unique to Philadelphia. The Annual Meeting gave me an excellent opportunity to network with students and professionals alike. The camaraderie and friendliness among the poster competitors was excellent, and I feel like I made some amazing friends through the conference. I also got to meet many of the people responsible for these events and for implementing ISPE's focus on YPs, and it was clear that they were very in touch with our interests as individuals and professionals. The Annual Meeting also gave me the opportunity to expand and develop professionally. I was able to participate in workshops beyond my experience and expertise, and felt nothing but support and inclusion from the others present. By talking with these professionals from a wide range of disciplines I managed to gain new perspectives on my own research and get a look at the industry ahead of me after my degree.

I think what really struck me about the ISPE Annual Meeting was how invested everyone was in the pharmaceutical industry. This industry is united behind a very powerful and motivating goal: to help people by developing better treatments. This cause goes very far to unite people across various disciplines, leading to some truly awe-inspiring innovation across the board.

Kirivann Chhoeun

The most wonderful part of the ISPE 2018 Annual Meeting was the networking—the meeting of minds and all the new friendships made with fellow students and even professionals. It was truly an incredible experience to be able to participate and represent the Boston Chapter at the Annual Meeting. The competition helped to build confidence and allowed students to practice presentation and communication skills. The different research projects gave me a different perspective on what the life sciences can entail as well as the different backgrounds that ISPE is able to bring together. Not only did I meet fellow students from the national chapters, I also made friendships with people from international affiliates and got to pick at professionals' brains and learn about their personal experiences abroad.

The conference tracks were very high level for students' knowledge base, in general. I attended most of the sessions for the Regulatory track, and it was very insightful. Most of the theoretical presentations were relevant to my personal studies, while other presentations were very involved and specific to certain manufacturing and regulatory practices. Just to hear the discussions and the types of questions asked by professionals during these sessions forced a student like myself to stretch my mind just a bit further to see what is over the horizon. It allowed me to see what different directions I may take my master's in regulatory affairs in the future.

I strongly recommend that students attend the Annual Meeting and maintain ISPE membership. The organization has so much to offer, including the knowledge base about upcoming and existing technologies and manufacturing practices. It was a privilege to be able to participate this year. I'm truly thankful for the opportunity!

Boonta Chutvirasakul

This opportunity allowed me to explore the beautiful and historic city of Philadelphia for the first time and also offered an incredible platform to learn and connect with many wonderful and talented people. It was my honor to earn this privileged opportunity. This platform has given me knowledge, connection, and transformation. ISPE community is warm, with many experienced professionals. They have delivered latest pharmaceutical trends and technology to move forward pharmaceutical products and precision medicines for patients' better quality of life. To achieve these goals, we cannot perform alone; we need help and support from everyone to make contributions to solve our current problems. I have found my passion is to be interested in real issues in pharmaceutical industry, and this driving force inspires me every day to perform what needs to be done to make a difference in our society. By presenting my work at the Annual Meeting, I learned and connected with other experts in many different fields. I was so grateful to have such insightful conversations with these wonderful people—to know who they are, what they do, and how they have overcome their struggles. This process has given me an opportunity to know and transform myself into who I want to be.

Mia Hall

The networking sessions and seminars were where I was able to get the most information about the industry and the different pathways people took. For example, at the first-timers' breakfast, three speakers told us how they went from where they started in the industry to where they are now. It was very interesting to see what I have in common as a graduate student with some of the professionals who have been working for many years in the industry. In one networking session, we did a "speed dating" activity for networking, and I really enjoyed that because I was able to talk with multiple people and ask questions and learn. The social events were a great way to top off the trip and wind down after attending the seminars. It was also a great way to keep networking in a less-formal way and get to know people's fun side.

Kinza Hussain

The ISPE app was a useful tool that I used daily during my time at the Annual Meeting because it allowed me to easily access the schedule and locations for several workshops. I attended the Young Professionals & Student Orientation Brunch, where I networked with YPs and received career advice from professionals in the industry.

On day 2, the other undergraduate and graduate student poster competitors and I stood by our posters in the Expo Hall. Many people came to our posters to learn more about our research. I appreciated this because it gave me the chance to present my research and network with distinguished individuals. It was also

great practice for our upcoming presentations to the competition judges. More importantly, I had the opportunity to learn about everyone else's research.

I thank the ISPE Foundation for awarding me the remarkable opportunity to attend the Annual Meeting. I will remember this experience for a lifetime, and I anticipate I will participate in upcoming meetings. The networking and informational sessions are a valuable experience that I can recommend to anyone in the fields of science or engineering. Thank you, ISPE, for adding value to my academic career and inspiring me to reach new heights in the future.

Nick Lewis

From getting exposure to a cutting-edge and impactful industry to staying in a city with rich American history, my time at the Annual Meeting was filled with experiences that I know will help me grow as a person. I love being involved with academic research, and I especially love sharing my research with all who are interested. The poster competition was a very meaningful experience that I will never forget. Not only did I get to share my work with others, but I also got to learn about what other students are researching. All the other poster presenters were friendly and conducting interesting work, making them great competition as well as good people to network with. The other presenters had a range of scientific backgrounds and came from across the US as well as other countries. This diversity allowed me to take a lot from the experience in terms of the actual science behind each presenter's research as well as from the social aspect of this experience. Having our posters up in the exhibit hall made me really feel like I was a part of the event, that I was a future professional among many current professionals.

The conference was huge, exposing me to so many people with so many different backgrounds. I enjoyed talking with the professionals about my research and their interests as well. This event exposed me to so many disciplines within pharmaceutical engineering that I had never been exposed to, allowing my potential career paths to expand.

Cy Rodriguez

The ISPE 2018 Annual Meeting completely exceeded my expectations in all aspects: the lessons I couldn't have learned anywhere else, the what-I-thought-were-impossible networks I gained, the treasured memories I made, and all the out-of-reach opportunities that were suddenly made available to me. Learning from leading experts about everything from the recent advancements in lifecycle process validation to Good Manufacturing Practices specially tailored for YPs was an experience I will never encounter inside a classroom. More importantly, I learned valuable lessons about the distinct views, professional interactions, and skills that encourage wholesome development as a YP. These were worth more than to the cost of attending this conference, although I was fortunate to have my registration and travel generously subsidized by the ISPE Foundation.

Nicole Rosselli

I have never attended an event even remotely comparable to the ISPE Annual Meeting. I met such incredible colleagues and professionals and made a handful of friends from all over the world. It gave me a unique opportunity to really get to know other people and learn from their experiences. It played such a major role in helping me figure out what I want to do once out of college. I was inspired after every conversation I had and felt encouraged to know all of the possibilities that await me. Overall, I also learned of an amazing society and group of people that I would like to associate myself with for the rest of my career. Every single person I met was so supportive of me as a young student and showed enthusiasm to help and mentor me in my future endeavors. ISPE creates a community of people who strive to encourage and strengthen each other in their careers. I was so inspired over the four days I spent at the Annual Meeting that I want to continue to engage with ISPE in the future, continue building the relationships I made, and eventually inspire others in the way I was inspired.

"Thank you, ISPE, for adding value to my academic career and inspiring me to reach new heights in the future."

Vishnu Sunil

Before the poster exhibitions began, I attended the Young Professionals & Student Orientation Brunch, where I got to meet my peers and discuss several ideas that I had in mind. The talks by the senior members were very useful, as they explained what ISPE is all about. They emphasized that we should use this opportunity not only to gain knowledge about the different aspects of the pharma industry but also to interact and network with industry professionals. It was interesting to hear their opinions on where the industry is heading and how as the young community, we can shape the future of the medtech/pharma industry.

This conference was very different from the ones I had attended previously; it was a very industry-focused conference. Hence, I got the opportunity to meet many of the big names in the industry. The positive comments that I received from people who approached me have motivated me to continue working harder than ever. ISPE organized many networking events in both formal and informal settings, from the Yard visit to the night at the Reading Terminal

Market. This was a wonderful opportunity to connect with fellow students and YPs who have just entered the industry.

The job fair held at the conference was very useful. I actually got two job offers! It gave me an idea about what the pharma companies need and how best to mold my skill set to address their requirements. I also received some great advice on which companies to approach.

Other than meeting a lot of like-minded and bright individuals, it was the judges' evaluations that I liked the most. They mentioned both positive aspects about my presentation and things that I could improve. I believe this feedback is very important to improve as a presenter.

Lilley Tran

From my trip, one of the many lessons that has resonated with me is the value of networking. Because ISPE is composed of professionals from all walks of life, the experiences and knowledge that are shared are priceless. Even as a new graduate, I realize that my journey and success are never achieved alone because there are others all around me in the same boat. Learning about people and getting to know how they got to a point in their life helps me understand more about the industry and what professional development is essential for growth. I would personally like to give a huge thank you to all the people who make ISPE what it is today. Your commitment is truly why I choose to be part of an amazing organization.

"Because ISPE is composed of professionals from all walks of life, the experiences and knowledge that are shared are priceless."

Melissa Wooten

In addition to socializing with colleagues from other institutions and a trip to one of the pertinent areas for pharmaceutical research, the three highlights of attending the Annual Meeting were hearing presentations during the workshops, presenting my own research, and conversing with other YPs. Going to the workshops informed me of what others are doing in a way that is clearer than the published paper because we had the ability to ask questions. The workshops also inspired research ideas of our own and exposed us to different roles that are needed in the pharmaceutical industry. I learned that listening to the talks is valuable, and that hallway conversations can be even more beneficial. Engaging with others in pharmaceutical industry is the priority to further improve patient lives because that is how ideas are shared.

The poster presentation was the opportunity tell others about my research. I had to think about how to frame my research topic to express how relevant it is. This is an important skill for me to develop not just for a conference but in general, as researchers are always having to express why their research is important. I was able to practice with my competitors (who became more like friends than competition) and then further refined my presentation during breaks and meals at the conference. I returned from the ISPE Annual Meeting more excited about my research than when I left. I was reminded that I am headed toward my career goals and others are excited for me. As I refined my presentation during the conference, I learned to talk first about the *goals* of my research, and then follow about the *techniques*. You have to convince others that the work is worth hearing about before they will be willing to listen to the technical details. I really learned how to "sell" the importance of my research.

About the ISPE Foundation

You can help to make other Travel Grant recipients' stories possible by contributing to the ISPE Foundation.

For more information on the Foundation and to contribute, go to https://ispe.org/initiatives/foundation

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FOYA Category Winners and Honorable Mentions for 2019: Best of the Best

By Marcy Sanford

Each year, ISPE celebrates innovations and advances in pharmaceutical manufacturing technology with its Facility of the Year Awards (FOYA) program. This year's nine category winners and honorable mentions range from industry giants with hundreds of years of history to relatively new enterprises. The projects spanned the globe, but all had a few things in common: their dedication to advancing technology to benefit consumers, their commitment to safety, and their desire to revolutionize the way things have been done.

FOYA 2019
Facility of the Year Awards

The Overall FOYA winner will be announced during the 2019 ISPE Annual Meeting & Expo on 29 October. The FOYA Celebratory Reception and Banquet will take place on the evening of Sunday, 27 October. For more information, go to https://ispe.org/facility-year-awards/foya-banquet.

EQUIPMENT INNOVATION: JANSSEN CILAG SPA

Adapting to Meet Consumer Needs

The Janssen Latina SpA factory site produces 3.8 billion tablets and capsules each year. Built in 1983, the factory has undergone renovations and additions over the years to adapt to market needs. One of those changes has been the use of new and innovative Dosepak packaging and I-Smart technology.

Janssen's engineers worked with external companies to create state-of-the-art equipment that is unlike any other in the industry. Previously, it took eight steps, three machines, and four production phases as well as two additional manual steps to produce an I-Smart Dosepak. The new equipment combines all the multiple steps and phases into one unique production process that integrates advanced robotics and automations into standard packaging process steps and allows Janssen Latina to launch new products with innovative packaging while keeping production processes lean, flexible, and sustainable.

"Overall, the Dosepak equipment makes the Janssen Latina plant ready to support the introduction of new lifesaving products with special packaging requirements," said Marco Minotti, Engineering Site Lead. "No other equipment combines standard wallet, Dosepak, and I-Smart handling in one single machine while also having the flexibility to process different products and a wide range of blister and wallet dimensions and reducing the amount of time needed to produce a unit. The equipment increases site capacity and reduces labor costs while being designed and built with the highest safety standards for its category. With this equipment, we are able to produce medicines in a more efficient and cost-effective way, ensuring higher quality and lower costs to patients."

FACILITY OF THE FUTURE: MODERNA, INC.

Creating Medicine of the Future

Since its founding, Moderna has become a leader in messenger ribonucleic acid (mRNA) research and development. Today, the company's pipeline includes mRNA-based investigational medicines for infectious diseases, immune oncology, rare diseases, and cardiovascular diseases. Currently, Moderna has 21 development programs in its pipeline. Anticipating rapid pipeline growth and recognizing the lack of external capacity to support the company's ambitious timeline, Moderna management decided in 2015 to construct a dedicated manufacturing facility in Norwood, Massachusetts.

Moderna designed the facility to be highly flexible, adaptable, and capable of manufacturing 100 GMP lots per year for the clinic as well as 1,000 mRNA orders per month. It leverages a "ballroom" concept, with equipment and digital tracking allowing for individual suites to be quickly and easily reconfigured for various uses based on demand. The company's approach to bringing digital technologies into its workflows and processes, using robotics, automation, artificial intelligence, and cloud-based computing to fulfill the cGMP operating strategy, brings the industry to a new level in the digital era.

"We are excited about the rapid progress we've made thus far at Norwood, and we continue to improve and optimize our processes," said Juan Andres, Moderna's Chief Technical Operations and Quality Officer. "Our goal is to ensure this facility fully supports our broad research and development objectives and timelines as we work to bring a new class of medicines to patients."

FACILITY INTEGRATION: PFIZER, INC.

Delivering Lifesaving Medicine

Pfizer, one of the world's premier innovative biopharmaceutical companies, was already distributing lifesaving cancer medications, monoclonal antibodies (mABs), to more than 100 countries, thanks to one biopharmaceutical center in Ireland and two in the US, when they decided to build another center in China. Globally, 7 of the top 10 best-selling medicines are biologics, and sales are growing; however, most people in China did not have easy access to mABs, with biologics accounting for only 4% of the medicines prescribed there.

Pfizer partnered with world-class companies and top local contractors from the beginning of the project and treated all partners as peers. They developed shared goals, and Pfizer encouraged a philosophy of mutual respect for all people. With an international effort from teams located in many countries around the world, the project was finished on time, under budget, and with an unparalleled safety record. "Our project was led by a small, experienced management team who were focused and empowered to make all decisions," said Chaz Calitri, Vice President for Pfizer Manufacturing Operations.

Industry cost, schedule, and safety records were broken as a result of the incredible commitment and dedication from the global execution team. The Pfizer project involved 3,700 people working more than 2.7 million hours with a perfect safety record and no lost-time accidents (the industry average for similar projects is eight lost-time accidents). The Hangzhou project cost of $195 million was significantly less than the cost for similar pharmaceutical projects in China, and the project was completed in 25 months, compared to an industry average of 36 to 60 months for comparable ventures.

OPERATIONAL EXCELLENCE: KANTONSAPOTHEKE ZÜRICH

Serving the Needs of a Growing Population

Kantonsapotheke is one of the leading centers of hospital pharmacies in Switzerland. Before Kantonsapotheke replaced and integrated two outdated hospital pharmacies for the Canton of Zürich hospital system, patients often had to wait a long time before receiving the medicine they needed. "The old facilities were not reliable anymore," said Heinz Obertüfer, a pharmacist, economist and pharmaceutical manufacturing leader in Zürich. "They had many deviations with the medicines, and it always took a long time to investigate and ensure that products were safe and reliable. Sometimes, they had to throw batches away; sometimes, they did not have the right product available."

In addition to setting up a new pharmaceutical building, Kantonsapotheke also reorganized the organizational setup to ensure Lean structures and clear responsibilities, incorporated

robotics to increase productivity, and redefined and reengineered all operational procedures and processing steps.

Now, the new compounding pharmacy offers a broad spectrum of pharmaceutical services, including oral, dermal, and parenteral formulations, often with patient-specific recipes, using the latest technologies and most up-to-date pharmaceutical knowledge. All products are manufactured under industrial cGMP conditions, and the operators have achieved an astonishing 60- to 90-minute turnaround time from diagnostic test to patient delivery.

"Kantonsapotheke will use this project as an example for future ones to improve and standardize manufacturing. The project lifts the basic concept of the hospital pharmacy into the scientific and technological future, creates a benchmark for other pharmacies around the world, and has quickly become a beacon for the way pharmaceutical therapeutics can be effectively delivered to patients," said Obertüfer.

PROCESS INNOVATION: ELI LILLY AND COMPANY

Launching a First-of-Its-Kind Continuous Manufacturing Facility

Continuous manufacturing (CM) offers new technologies to pharmaceutical manufacturing and new opportunities for safer and greener chemical processes. Eli Lilly and Company has been recognized as an industry leader in this transition. Lilly's small-volume continuous (SVC) facility combines the practicalities of small-scale processing with the innovations of CM technologies to quickly deliver active pharmaceutical ingredients (APIs).

Before Lilly's SVC facility, no other company had simultaneously applied CM technology to the production of multiple process steps, including all process separations steps and API crystallization. The guiding principle of the SVC facility is that several GMP steps are coupled together so that one step flows seamlessly to the next and all can run at the same time. This allows Lilly to have a much shorter cycle time compared to traditional batch processes and makes the facility more responsive to supply chain demands to meet patient needs. The facility was used to manufacture APIs for clinical trials of one of Lilly's potential new cancer drug candidates. This took place in conditions that were safer and more productive than a batch process, and the fully continuous process yielded the first batch of APIs after 2 weeks rather than 2 months.

"This new facility means that Lilly research and development can apply the most innovative approaches to design of continuous processes, in the knowledge that these medicines can now be manufactured with better chemical reaction safety than previously possible," said Martin Johnson, Senior Engineering Advisor, Small Molecule Design and Development for Eli Lilly.

"The project lifts the basic concept of the hospital pharmacy into the the scientific and technological future and creates a benchmark for other pharmacies around the world."

PROJECT EXECUTION: PFIZER, INC.

Executing on Time and on Budget with a Perfect Safety Record

In 2015, Pfizer decided to construct a state-of-the-art greenfield biotechnology center in Hangzhou, China, to serve the underdeveloped biologics market in the country. The $195 million project had many challenges, but thanks to a team-centered approach that focused on communication, collaboration, and delivery, Pfizer was able to meet and exceed their goals.

They broke ground in 2016, and 25 months later what had once been an empty field was home to a state-of-the-art drug substance and product manufacturing facility with single-use disposable technology and an integrated lyophilizer and filling line, as well as a high bay warehouse, a central utility building, administrative offices, laboratories, and a cafeteria.

The Hangzhou Global Biotechnology Center was completed with a perfect safety record; there were zero lost-time injuries

2019 ANNUAL MEETING & EXPO

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John Crowley
Chairman, Chief Executive Officer, and Co-Founder
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William Anderson
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Connecting Pharmaceutical Knowledge

> "With this innovative project in energy efficiency, our people feel they are working in a facility that can help to put our planet on the path to sustainable development."

during 2.7 million hours of site activity. The project team trained 3,700 workers on Pfizer's safety program. Additionally, the project was completed on time and on budget.

"When asked why this project is viewed as such a success, the overwhelming response is that it all starts with the team," said Chaz Calitri, Vice President for Pfizer Manufacturing Operations. "From the beginning of this project, we knew that the only way to overcome the challenges was to build and empower a small, talented team from inception to startup. They were empowered to make decisions. We used local talent as much as possible, and this helped with language, culture, and training."

SUSTAINABILITY: CELGENE INTERNATIONAL II

Reaping Long-Term Rewards of a Commitment to the Environment

In 2015, while developing plans for a facility that would be able to meet the growing demand for their existing products and future needs for developing technologies, Celgene made a pledge to apply environmentally sustainable philosophies throughout the design and create a facility where sustainability was ingrained in daily operations.

The site was conceived, designed, and built with a superior energy concept for water heating and cooling, and state-of-the art, energy-efficient equipment and materials were used throughout.

Celgene's unique and innovative energy-efficient concepts reduced carbon dioxide output to 1,400 metric tons per year, which is 70% less than output for a standard installation and building construction. Celgene's total heat requirements are 22% less and their cooling needs 13% less than those of other comparable buildings. Overall, thanks to their forward-thinking measures, the total final energy consumption to meet Celgene's requirements is 53% less, and the total need for fossil energy (natural gas and fuel oil) is 60% less than that of a standard building.

"With this innovative project in energy efficiency, our people feel they are working in a facility that can help to put our planet on the path to sustainable development. They are proud to share this outstanding realization with their families and our local communities," said Jacques Soguel, Vice President, Global Engineering & GMP Facilities. "In addition, optimizing our energy usage not only decreases the use of natural resources, but we also see the benefit of reduced electrical costs compared to other manufacturing sites."

HONORABLE MENTION: AVEXIS, INC.

Making Gene Therapy History

Founded in 2013, AveXis, Inc., is a gene therapy company dedicated to developing and commercializing novel treatments for patients with rare and life-threatening neurological diseases. Once AveXis was ready to ramp up production of AVXS-101, a one-time-dose gene replacement therapy for infants born with spinal muscular atrophy, they knew they needed to build a state-of-the-art manufacturing facility.

They were able to do so with innovative execution while meeting the deadlines of a very aggressive timeline. AveXis did not have the benefit of case studies to follow and had to forge their own way. They decided to use equipment that had previously only been used for research and development and to partner with the suppliers to revamp the equipment. Much of the equipment had to be customized or completely redesigned for the facility. The unique manufacturing facility includes modular, single-use technology and cutting-edge manufacturing equipment and systems that are among the first of their kind in the industry.

At the new facility AveXis can produce gene therapies for commercial distribution and ongoing and future clinical trials. Additionally, manufacturing gene therapies in-house provides AveXis with much-needed control, gives them the ability to make decisions quickly, and decreases production costs.

HONORABLE MENTION: TAKEDA

Fighting Rare Diseases

Every year, millions of patients depend on plasma-derived therapies obtained through plasma fractionation processes. To meet the growing global need for these lifesaving therapies, Takeda built a 1.1-million-square-foot manufacturing facility on 160 acres in Social Circle, Georgia, US.

The Georgia manufacturing facility is one of the largest greenfield site projects in the United States and one of the largest plasma fractionation sites in the world. The facility is licensed by the US Food and Drug Administration for distribution in the United States, and Takeda has future plans for licensing and distribution into China and European markets.

To successfully build a project of this scale, subject matter experts from around the world collaborated to design, develop, and construct the state-of-the-art facility. In this unprecedented collaborative effort, Takeda relied on an exemplary management team, innovative risk management strategies, and excellent communication to keep the project moving forward.

In addition to having the capability to meet Takeda's production goals, the facility positively impacts the wellness of employees and was built with a stellar safety record.

About the author

Marcy Sanford is an Editorial Assistant for ISPE.

FOYA Category Winners and Honorable Mentions

Equipment Innovation:
Janssen Cilag SpA

Facility of the Future:
Moderna, Inc.

Facility Integration:
Pfizer, Inc.

Operational Excellence:
Kantonsapotheke Zürich

Process Innovation:
Eli Lilly and Company

Project Execution:
Pfizer, Inc.

Sustainability:
Celgene International II

Honorable Mention:
AveXis, Inc.

Honorable Mention:
Takeda

2019 ISPE Biopharmaceutical Manufacturing Conference

WOMEN IN PHARMA® FOCUS ON BALANCE

By Susan Sandler

The second day of the 2019 ISPE Biopharmaceutical Manufacturing Conference in Boston, 18–20 June, kicked off with the Women in Pharma® Balance for Better in Biopharmaceutical Manufacturing breakfast session. Session leader **Katherine Leitch**, Director of Technical Services, External Manufacturing, Alexion, led a discussion with four other panelists:

Christina Broomes, Director, Contract Manufacturing, Ultragenyx Pharmaceutical

Tom Jede, Site Head/Senior Director, Vector Manufacturing, bluebird bio

Anne Kantardjieff, Director of Plasmids and Small Molecules, bluebird bio

Whitney Kutney, PhD, Vice President, Operations, ValSource

After each panelist presented, breakout sessions gave attendees the opportunity to offer their input into a range of questions posted for discussion.

PASSION FOR DIVERSITY

Broomes stressed that her passion for engineering is combined with a passion for diversity. She shared her journey into engineering, which began in high school, as an illustration of how to support diversity in engineering.

Left to right: Whitney Kutney, Anne Kantardjieff, Tom Jede, Christina Broomes, Katherine Leitch, and Vivianne Arencibia, Independent Consultant, Arencibia Quality Compliance Associates, who introduced the session.

In response to the question, "In your experience, what are unique challenges in a manufacturing environment for working parents and how have you overcome them?" she said, "You learn as you go what's best for you." Her work in internal manufacturing could require 24/7 availability, but there are solutions that relieve the demands and allow time for having a family. She recommended, "Build relationships—internally, direct reports, peers, management. Understand that we all are human, and we are not available all hours of the day." Communication as you build coverage is essential to ensure that the manufacturing operation can keep going but individuals can have a break. "You need balance, so you are not always on call," she said. "It is important for people inside and outside of work to show that you can balance."

LEADING BY EXAMPLE

Jede provided background on his own career and noted that he has been an ally and supporter of women and diversity in various workplaces because he experienced unique and diverse leaders as he was moving up. Building teams that are both great and diverse

is important to him, and this value is shared at his current company, bluebird bio, which emphasizes family, future generations, and improved quality of life. His commitment to diversity has also been inspired by strong women in his personal sphere, including his grandmother, who came from Germany and built a career in manufacturing; his wife, a women's studies major in college; and his daughters.

In response to a question about the benefits to a leader of having diverse teams, Jede said, "I have worked in startups, bringing new teams together, building the culture for what we want the startup to be. I've learned the benefit of having different perspectives." He noted that the key leadership team at bluebird has equal numbers of women and men. He also highlighted the importance of team members feeling that their voices are heard and respected, employees having role models on the leadership team, and colleagues being able to rely on each other's strengths. "At bluebird, people at all levels are emulating behaviors of strong female leaders, and this will benefit us over the years."

BEING A ROLE MODEL

Kantardjieff moved from a chemical engineering career into manufacturing. Her mother, who was an engineer, was her role model, and so engineering "was always what I wanted to do." Now, Kantardjieff wants to be a role model for her two daughters and the industry, to inspire more women to become involved in science, technology, engineering, and mathematics (STEM).

When asked what advice she would give other female technical leaders to reach their full potential, she said, "Advocate for yourself. No one cares more about your career than you do." After being told this early in her career, "that advice made me understand that I needed to be more vocal about the opportunities I wanted," she noted. "I have grown in those roles where I was 'voluntold' or able to do something outside my comfort zone."

Kantardjieff also advised engineers to grow their professional networks, suggesting that involvement in ISPE and other professional organizations is a great way to do this. Having mentors is also critical—when approaching someone to be your mentor, be clear on the time commitment and what you hope to get out of the mentorship, she said.

Finally, whether you are a woman or a man, the two most important competencies to develop are self-awareness—understanding strengths and areas you can develop—and agility. Opportunities may be a little different, and you need to be comfortable in taking on the challenge to something a little different. Kantardjieff looks for this trait in new team members.

SETTING AN EXAMPLE

Kutney also is a chemical engineer who has moved into biotech. She wants her three children "to understand there are no constraints to them or their careers." She was asked if she could go back in time and give herself advice, what would she say about women leaders in technical roles, and she replied that balance is key. "There is a way to manage everything. Understand your priorities, based on what is most important to you. Especially as a manager, someone else's emergencies do not necessarily need to be your emergencies."

"Don't be afraid to make mistakes," she emphasized. "Learn from them, this is most important. Escalate at the right time as needed. Ask for help." Encouraging other team members is also very important, as is finding a manager or mentor who is interested in discussing your career and your advancement. Start to identify and train your replacement early in a job, so that you are able to move on to your next position when you are ready.

IDEAS FROM BREAKOUT DISCUSSIONS

- Help your team to identify opportunities that are good fits for their goals, things they are good at—individual plans are important.
- It's not what what you know, it's who knows you. In other words, become known so you will be asked to participate in projects.
- Be a mentor; have a mentor.
- Speak up: This gets easier as you become more established in your career.
- Work-life balance is for everyone (not just parents). Don't apologize for needing this balance.
- Better communication makes life easier.
- Educate kids at an early age, even in single-digit ages, to get them involved with STEM.
- Your core values remain the same no matter where you are in your life or career. Trying to find a work-life balance is key to achieving your goals, whatever they are, at different stages of life. Rely on strong support systems to help get you there; also, rely on who you are and what's important to you.
- Set boundaries. Let people know how you expect to be treated, so people can treat you that way.
- Stay calm under pressure.
- Take responsibility—volunteer for tasks, and then deliver. People see what you are doing and make judgments.
- People have weaknesses; be honest about yours.
- Companies need a family-friendly human resources policy, with equal family leave and maternity/paternity leave opportunities for women and men.
- Senior leaders need to set a standard. Leaders who take time off for vacations, to attend their kids' soccer games, or for a doctor's appointment show the people they manage that they can do the same.
- Leadership needs to support change, and put structure around it, through initiatives such as diversity weeks and women's career networks. These efforts make diversity a part of the workplace.

About the author

Susan Sandler is the Editorial Director of *Pharmaceutical Engineering*.

ISPE BRIEFS

New CoPs Platform to Offer New Capabilities and More

ISPE will introduce a new platform this fall for online Communities of Practice (CoPs) that will make the CoPs more useful and user-friendly. Participating in a CoP by posting a question or responding to a post is a great way for ISPE members to meet colleagues from all parts of the world and exchange or gain knowledge.

The new CoP platform will have enhanced posting capabilities, making discussions even more useful and robust. Participants will be able to include images within a discussion post to help illustrate a point or give a visual reference when asking for advice. The new platform will also make it easier to follow discussions, recommend discussions to others, and save discussions for later reference. Also included will be an improved search function and enhanced networking features such as personalized user profiles and the ability to link to other social media profiles.

ISPE has 16 CoPs in a variety of areas, including Biotechnology, Critical Utilities, Commissioning and Qualification (C&Q), GAMP®, and Project Management. Go to https://ISPE.org/Membership/Communities-Practice for more information about CoPs or to become a member of a CoP. Please email ask@ISPE.org if you have any questions about the new platform.

—Marcy Sanford, Editorial Assistant

Panel Celebrates College's First Biomanufacturing Graduates and Career Planning

On 22 April 2019, more than 40 professionals and students attended the ISPE Solano Community Advisory Panel at Solano Community College in Fairfield, California. This event was in honor of the first graduating class from the Solano Community College Bachelor of Science Program in Biomanufacturing.

The event focused on industry trends, as well as career opportunities for both novice and established professionals. Panelists included Sri Gavini, Business Development Manager, Process-West Coast, Emerson Automation Solutions; Kim Ngan Huynh, Quality Control Associate, Genentech; Paul Lauer, Strategic Facilities Advisor at Business Development Connections; and Cassy Gardner, Group Engineering Manager, Banks Integration Group.

Key points from the panel included the importance of identifying a mentor in your company; maintaining excellent interpersonal working relationships with coworkers; the benefits of seeking out and taking advantage of opportunities offered; and the value of face-to-face interactions and connections with future potential employers. Cell therapy and automation were industry sectors identified as areas for future career growth.

CALL FOR ARTICLES in 2020: SUBMIT YOUR ARTICLE TO PE

PE is always looking for great technical articles, features, and editorials on topics of interest to members. Check out the author guidelines and more for submissions at https://ispe.org/pharmaceutical-engineering/about/submit-article. **New:** The 2020 Editorial Calendar with themes has been posted at https://ispe.org/pharmaceutical-engineering/about/editorial-calendar. Your article does not have to be related to an issue's theme, although we welcome submissions on theme. Contact Susan Sandler at ssandler@ispe.org for more information.

We'd like to feature your chapter, affiliate, or other ISPE group in an upcoming ISPE Briefs! Share highlights from training programs, conferences, social events, or other activities with other ISPE members in an article of 250 to 400 words. We welcome photos, too; these should be 300 dpi or >1 MB. Send your submissions to Susan Sandler, Editorial Director, at ssandler@ispe.org.

INTERPRETATION OF VARIANCE COMPONENTS

for Blend and Content Uniformity

by Thomas Garcia, Angela Kong, and Fasheng Li

Despite introducing modern analytical technology to assess blend uniformity, many companies are still using traditional blend sampling thieves and wet chemistry to assess blend homogeneity. The use of statistically based sampling plans allows variance component analysis to be conducted on both blend and dosage unit data. This article shows how various combinations of blend and dosage unit variance components ("within-location" and "between-location") can be interpreted to identify potential root causes for homogeneity issues, including sampling bias, and how they can be mitigated.

SAMPLING PLANS

In August 2013, the US Food and Drug Administration (FDA) published a Q&A that included the expectation to test a set of three replicate samples that are taken from at least 10 locations in the blender when assessing blend uniformity [1]. The FDA also expects that variance component analysis (VCA) be performed on the data to demonstrate uniformity of the mix throughout the blender [2, 3]. In the 2013 communication, the FDA stated that USP Chapter <905> "Uniformity of Dosage Units" should not be used to release commercial batches of solid oral dosage forms, recommending instead the use of statistically based acceptance criteria to ensure that USP Chapter <905> is passed throughout the product life cycle.

The use of statistically based sampling plans allows VCA and comparisons to be performed on blend uniformity and content uniformity data of the subsequent dosage forms made from the blend. The standard deviations based on percentage of intent for blend and percentage of label claim for unit dosage are broken down into within-location variance and between-location variance. Within-location variance assesses the variability of replicate samples within a single location. Between-location variance assesses the variability across either (a) the sampling locations throughout a blender for the blend or (b) the sampling times throughout the compression or encapsulation/filling process. This technique can be applied at any stage of the product life cycle.

Statistically based sampling plans should be used to assess both blend uniformity and dosage form content uniformity, especially during formulation and process development. Sampling plans should take a minimum of three samples from each sampling location in the blender or sampling time point during the compression run. This allows statistical analysis to be performed on the data, and the results can be used to characterize the batch quality and assist in identifying potential causes for blend and content uniformity issues. For blend sampling, triplicate blend samples should be taken and assayed from at least 10 locations throughout the blender. Fewer locations can be used for smaller batches, with justification. The number of locations to be sampled for the dosage units depends on the batch size [2, 4]. However, at least triplicate samples should be taken from each location, including at the beginning and end of the run.

BLEND SAMPLING TECHNIQUE

Poor blend uniformity is often attributed to sampling bias, which is often the result of poor technique to extract the sample from the blender, and subsequent mishandling prior to analysis. Ideally, it would be convenient to use a single blend sampling procedure for all products (thief design, sample weight, sampling locations, etc.). However, there is no guarantee that a single sampling technique can be used across products. Different blends have different characteristics, which may require developing a product-specific blend sampling procedure. A "good faith" effort to develop a sampling technique should be demonstrated prior to defaulting to the use of dosage units as a surrogate for blend uniformity.

Developing a blend sampling technique may consider the following aspects:

- Minimize operator-to-operator variability by ensuring that operators taking blend samples are properly trained.
- Define a sampling plan that provides coverage throughout the blender and includes known areas of slow material movement in the blender (i.e., dead spots).
- Ensure the sampling technique considers the type of thief (plug or chamber, material of construction, etc.), as the type can impact thief performance and results. Plug thieves pull stationary samples and eliminate potential segregation of the sample as it flows into the chamber.
- Determine whether to wipe the thief between samples. Residual material inside of the thief should always be removed between samples.
- Define the angle of insertion and cavity chamber position in the blend for chamber thieves. Triplicate samples from each location should be taken close to each other, but the thief should never be inserted into the same spot multiple times.
- Ensure the sample size is one (1x) to three times (3x) the dosage unit weight. If sampling bias is still evident at 3x, it may be necessary to use a different type of thief and/or identify the smallest sample quantity beyond 3x that reduces sampling bias and provides data similar to the drug product results. One example where this may occur is for low-weight tablets (~50–100 mg). Sample sizes smaller than 150 mg tend to be more prone to bias, and 3x or greater quantities may be required.
- Assay the entire sample; do not subdivide the sample. If possible, discharge the sample directly into labeled, pre-tared containers to minimize powder transfers during sample preparation.
- Be aware of the impact that static charge may have on the sampling process. Grounding the bin prior to sampling may be required to allow the charge to dissipate.
- Develop detailed blend sampling operating procedures in addition to the sampling plan to ensure consistency and repeatability.

INTERPRETATION OF BLEND AND DOSAGE UNIT VARIANCE COMPONENTS

Once a rigorous statistically based sampling plan is implemented (either replicated sampling for a blend or stratified sampling for a drug product), VCA can be performed. The variation of the blend potency or the content uniformity of the dosage units can be broken down into between-location variation and within-location variation. Throughout this article, the total variation is noted as total variance or total standard deviation (i.e., the square root of total variance), the between-location variation is noted as between-location variance or standard deviation, and the within-location variation is noted as within-location variance or standard deviation.

For balanced sampling plans (i.e., plans with equal number of samples at each of the locations), method of moments can be used to estimate the variance components. Assuming there are B locations, and n samples tested at each of the B locations for content uniformity, x_{ij}, $i = 1, 2, \ldots, B$; $j = 1, 2, \ldots, n$. The mean and variance at each location can be calculated as $\bar{x}_i$ and s_i^2, $i = 1, 2, \ldots, B$; the variance of between-location means is $s_{\bar{x}}^2$.

The within-location variance $(\hat{\sigma}_\varepsilon^2)$ can be estimated as the mean, $(\sum_1^B s_i^2)/B$, of variances at each location. The between-location variance $(\hat{\sigma}_B^2)$ can be estimated as the variance $(s_{\bar{x}}^2)$ of location means minus the within-location variance divided by n, $(\hat{\sigma}_\varepsilon^2/n)$. In summary:

Within-location variance: $\hat{\sigma}_\varepsilon^2 = (\sum_1^B s_i^2)/B$
Between-location variance: $\hat{\sigma}_B^2 = s_{\bar{x}}^2 - \hat{\sigma}_\varepsilon^2/n$
Total variance = $\hat{\sigma}_B^2 + \hat{\sigma}_\varepsilon^2$

As an example, Table 1 illustrates the detailed calculation of variance components using the method of moments. For more general calculations of variance components calculations, please see references 3 and 5.

Table 1: Illustration of variance components analysis for a balanced sampling data set.

	Sample Potency (%)			At Each Location (n = 3)	
Sample Location	A	B	C	Mean ($\bar{x}_i$)	Variance (s_i^2)
1	97.8	97.2	95.2	96.73	1.80
2	97.9	99.1	98.9	98.65	0.39
3	98.1	101.8	103.3	101.07	7.01
4	99.8	103.0	101.7	101.49	2.47
5	99.7	100.9	100.3	100.31	0.32
6	98.6	100.8	99.2	99.54	1.25
7	99.8	98.8	98.8	99.12	0.31
8	102.7	100.4	105.9	102.98	7.61
9	101.2	102.0	103.6	102.26	1.42
10	97.4	99.2	101.0	99.20	3.23
Variance of location means: $s_{\bar{x}}^2$				3.49	
Variance (within-location): $\hat{\sigma}_\varepsilon^2 = (\sum_1^B s_i^2)/B$				2.58	
Variance (between-location) = $\hat{\sigma}_B^2 = s_{\bar{x}}^2 - \hat{\sigma}_\varepsilon^2/n$				2.62	
Variance (total): $\hat{\sigma}_T^2 = \hat{\sigma}_B^2 + \hat{\sigma}_\varepsilon^2$				5.21	
Standard deviation (within-location): sqrt($\hat{\sigma}_\varepsilon^2$)				1.61	
Standard deviation (between-location): sqrt($\hat{\sigma}_B^2$)				1.62	
Standard deviation (total): sqrt($\hat{\sigma}_T^2$)				2.28	

It is useful to plot blend and drug product content uniformity data at the start of analysis, as plots can identify variability and trends in the data. Scatter plots for scenarios often encountered have been previously published [6]. Figures 1–4 are examples of plots that can be associated with low within-location and between-location variances (i.e., a uniform blend), high within-location variance (poor mixing on a unit dose scale—poor

Figure 1: Plot showing low within-location and between-location variances (i.e., a uniform blend).

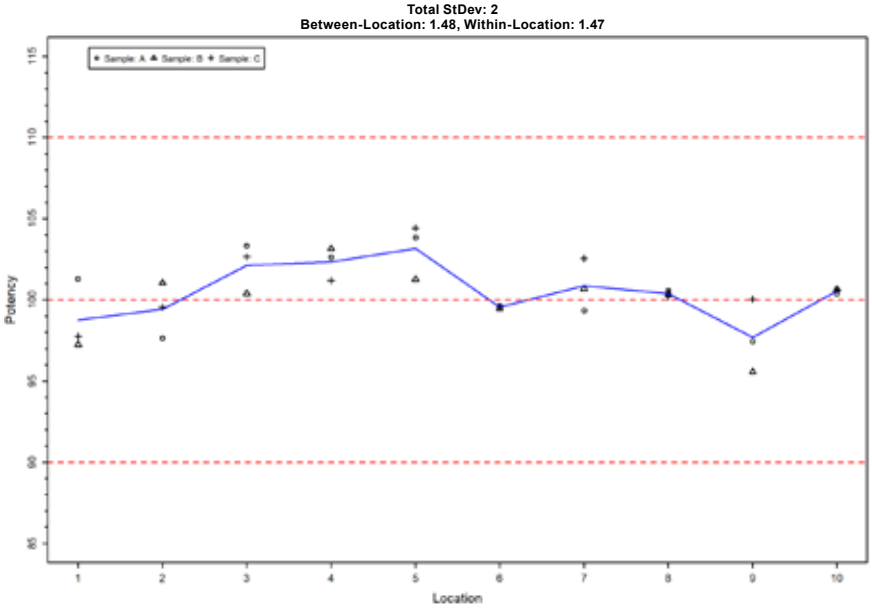
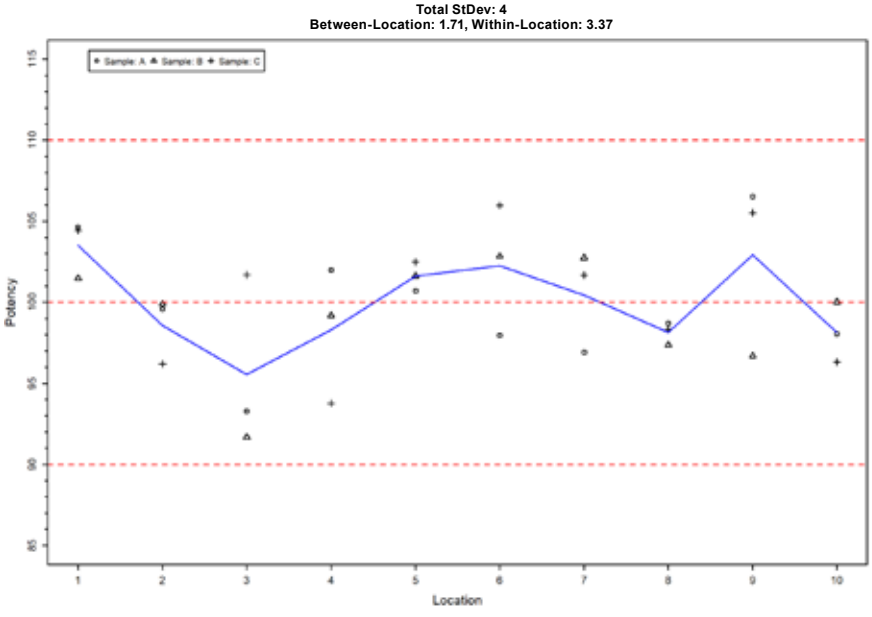


Figure 2: Plot showing high within-location variance (poor mixing on a unit dose scale–poor micromixing).



micromixing), high between-location variance (hot and cold spots in the blend—poor macromixing), and both high within-location and between-location variance (incomplete mixing).

Note that the assignment of "high" or "low" labels for variance magnitude in this article is subjective. The reader should consider product risks for "high" and "low" labels for variance components, which may include the magnitude of the overall standard deviation, drug load in the formulation, historical behavior of the process, the drug's therapeutic index, and other conditions. The dominant component is designated "high" and the minor component is "low." The designation is qualitative and does not take into account the total variance. However, a "high" label for blend and content uniformity data with a high total standard deviation (for example 6%–7%) is more concerning

Figure 3: Plot showing high between-location variance (hot and cold spots in the blend—poor macromixing).

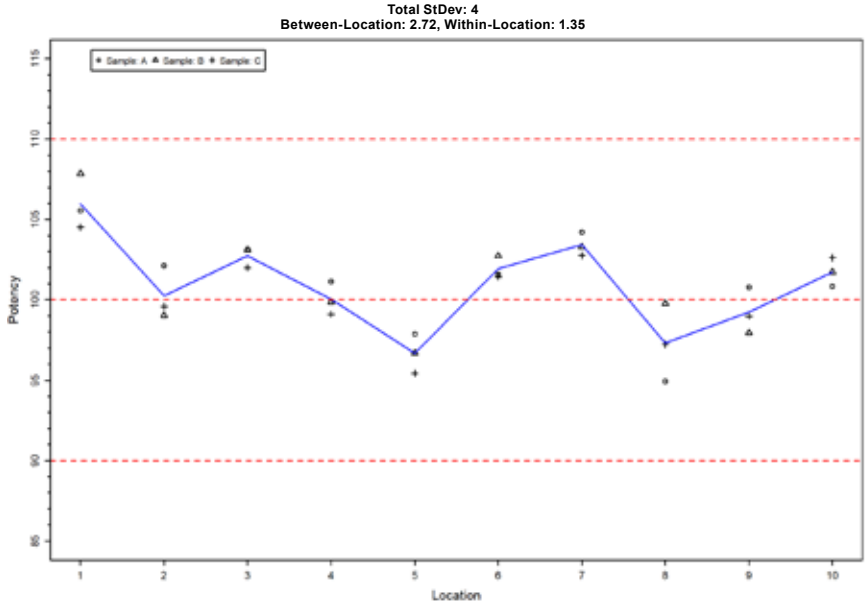
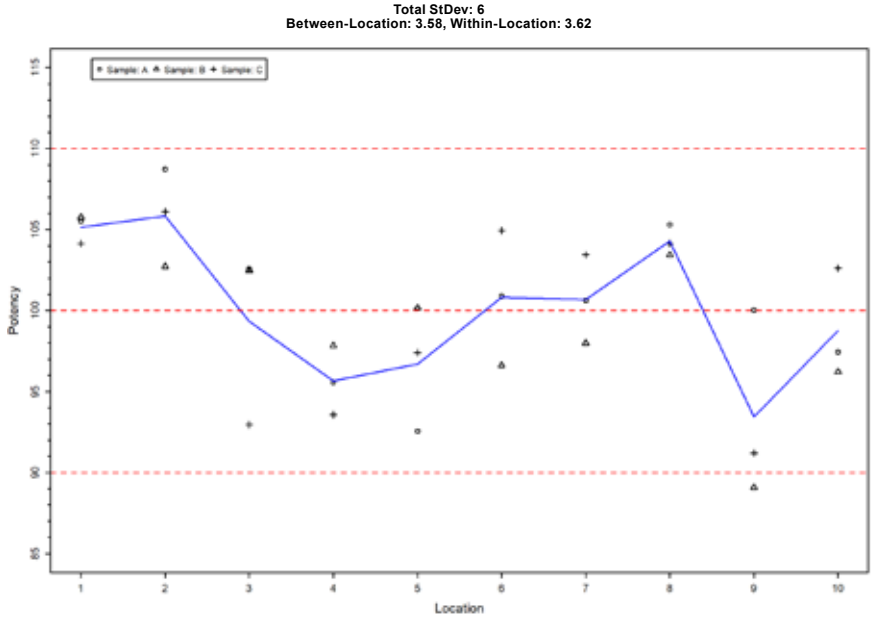


Figure 4: Plot showing both high within-location and high between-location variances (incomplete mixing).



than a "high" label for a batch with a total standard deviation of 3.5%. If the total variance can be attributed equally to within-location variance and between-location variance, both variance components are contributing to the overall variation for the product.

For the purpose of this article, standard deviation values are "rules of thumb"; standard deviations ≤3.0% for potency (based on percent label claim) are considered of acceptable uniformity for both blend and drug product uniformity without further analysis [2]. In some cases, performing VCA for batches with standard deviations ≤3.0% could be an overanalysis of the data. If the overall standard deviation is >3.0% for the blend and/or dosage units, VCA can be useful to help identify potential causes contributing to the nonuniformity. It should also be noted that multiple lots of blend and dosage unit data should be included in the investigation.

Table 2: Interpretation of variance components in blend and dosage units.

Blend		Dosage Unit		Interpretation
Within Location	Between Location	Within Location	Between Location	
Low	Low	Low	Low	Both the blend and tablets are uniform. Variability between and within locations is low.
Low	Low	Low	High	Blend is uniform. Segregation may occur during compression or filling at one or more locations. Plot stratified dosage unit data to identify where segregation is occurring. Implement controls and corrective actions.
Low	Low	High	Low	Blend is uniform. Agglomeration may be missed during blend uniformity analysis. Further agglomeration of the drug substance during blend transfers to the filling/compression process due to the poor flow. Apply blend-mill-blend process; improve powder flow during transfer to reduce the agglomeration tendency.
Low	Low	High	High	Blend is uniform, but the uniformity of dosage units may not be acceptable. Significant segregation and/or agglomeration of the drug substance may be occurring. Flow of the blend into compression/filling equipment may be poor. Plot stratified dosage unit data to identify signs of segregation or agglomeration. Implement controls and corrective actions.
Low	High	Low	Low	Initial mixing is incomplete, with possible downstream mixing in the feed frame during the compression/filling process. There may be dead spot(s) in the blender, or a mechanically induced hot spot (e.g., drug substance fines settling in a fluid bed dryer or falling out of a filter) may create a drug-enriched top layer in the blend. Identify the cause and implement controls and corrective actions for the mixing process.
Low	High	Low	High	Mixing in the blender is incomplete, which carries over to the compression or filling operations. Neither the blend nor the dosage units have acceptable uniformity. Evaluate mixing efficiency. Plot blend and dosage unit data to identify where segregation may be occurring. Implement controls and corrective actions or optimize formulation.
Low	High	High	Low	Blend is not uniform and likely has hot/cold spots. Some mixing may occur during the compression or filling process, but it is not enough to provide sufficient uniformity on a unit dose weight scale, resulting in high tablet-to-tablet variability for a given location. Flow of the blend into dies and filling equipment may be poor. Implement corrective actions controls for the blending step.
Low	High	High	High	Blend uniformity is unacceptable due to incomplete mixing in the blender. The poor blend uniformity is carried over to the dosage units, producing tablets that do not have acceptable content uniformity. Plot stratified dosage unit data to identify the presence of agglomeration or whether segregation is occurring. Fixing the blend is the priority. Implement controls and corrective actions for the formulation and manufacturing process.
High	Low	Low	High	Uniformity throughout the blender is acceptable. However, the high within-location variance may be due to blend sampling bias, agglomeration, or insufficient mixing on a unit dose scale. Segregation of the blend during material transfer (especially at the very beginning and/or end of the compression/filling of the batch) may be occurring. Plot stratified dosage unit data to identify whether segregation is occurring. Implement controls and corrective actions for the formulation and manufacturing process or the sampling procedure.
High	Low	High	Low	Agglomeration of the drug substance occurs during mixing, which carries over to compression/filling process. Mixing on a unit dose scale is incomplete. Identify the cause and implement controls and corrective actions for the mixing process.
High	Low	High	High	Uniformity throughout the blender is acceptable. Because the high within-location variance is carried over to the dosage units, blend sampling bias is ruled out; insufficient mixing on a unit dose scale may be an issue, and segregation of the blend during material transfer at very beginning and /or end of the filling or compression process may be present. Agglomeration of the drug substance may also be occurring. Plot blend and dosage unit data to identify where segregation may be occurring. Implement controls and corrective actions. Statistically based acceptance criteria should be used for batch release until process improvements and controls are implemented.
High	High	Low	Low	Either the blend is not uniform and downstream processing (e.g., milling) results in uniformity, or the blend data are biased due to sampling technique/error. An investigation should be performed for the blending process and sampling method/procedures. Implement controls and corrective actions accordingly.
High	High	Low	High	The uniformity of both the blend and dosage units is unacceptable. The formulation or process (or both) needs to be redesigned.
High	High	High	Low	Blend is not uniform. Some mixing may be occurring in the feed frame, resulting in acceptable average potency across the batch. However, there is considerable tablet-to-tablet variability from a given location. Agglomeration and segregation may be occurring in the blend. The formulation, blending, and compression/filling steps must be improved.
High	High	High	High	Blend and dosage units are not uniform. The formulation and/or blending and compression/filling processes are inadequate. The formulation, blending, and compression/filling steps need to be redeveloped.

Table 2 presents combinations of blend and dosage unit within-location and between-location variance components and examples for the interpretation of various combinations of variance components. The table is not meant to be comprehensive, as other interpretations of the data may be applicable. As noted previously, the terms "high" and "low" are used in a relative manner in this article; they are only representative of a particular data set.

SOURCES OF VARIABILITY AND THEIR MITIGATION

Potential sources of variability that can affect blend and content uniformity include incomplete mixing, segregation, raw material characteristics, agglomeration, and blend sampling bias.

Incomplete Mixing

Incomplete mixing results in a blend that has poor homogeneity. When this happens, the total standard deviation is high (for example, 5%–6% or greater) and may be split evenly between the within-location and between-location components. Table 3 identifies possible causes of incomplete mixing and strategies to resolve these issues.

Segregation

Segregation is a common issue that often occurs during material transfer, especially at the beginning (initial drop of blend onto the tablet press or filling equipment) or end of the batch during compression. Even though the initial blend is uniform, the expansion and movement of particles can result in separation of the drug and particles. This demixing often produces a high between-location variance component for the dosage units. Table 4 identifies potential causes of segregation and strategies to address these issues.

Raw Material Characteristics

Raw material attributes that have the potential to impact the mixing process and uniformity of the blends and drug product should be identified during formulation development. It is difficult to produce and maintain uniform blends without the proper characterization of the input raw materials.

It is important to select excipient grades that have similar physical properties (particle size, shape, and density) to those of the drug substance. Flowing powders with different particle size distributions can segregate. The particle size of excipients should be aligned with the drug substance, if possible.

Processes and equipment should also be designed to produce and maintain uniform blends. How the materials traverse through the process equipment train must also be understood. A drug-enriched layer may form on top of a blend due to the suspension of fine particles that settle out slower than granules at the completion of mixing. Fine particles of the drug substance that adhere to filter socks (e.g., fluid bed dryers and high shear mixers) can also form a drug-enriched layer on top of the mix. Subsequent blending (lubrication) may remix the fines. The final blend should be assessed for uniformity.

Table 3: Potential causes of incomplete mixing.

Cause	Mitigation Strategy
Mixing process is insufficient to produce a uniform blend; possible demixing	Optimize the blending process and process parameters.
Insufficient shear being applied to the powders with high cohesion	Use a higher shear mixer.
Limited room for the powder bed to expand during blending	Adjust fill volume if operating at the high or low capacity of the blender.
Poor formulation	Select excipient grades similar to the physical properties of drug substance, such as particle size.

Table 4: Potential causes of segregation.

Cause	Mitigation Strategy
Equipment design and setup	Reduce vibration during compression and filling operations. Minimize free-fall distance between bulk container and tablet press, or other filling machine. Use decelerators to prevent free fall of powders during transfer.
Manufacturing processes that directly blend the drug and excipients (e.g., direct compression); these processes are more prone to segregation, especially for low-dose products	Use wet and dry granulation processes to densify the blend and "lock" the drug substance and excipient particles together. Mill the granules to a consistent particle size distribution.
Poor powder flow out of the bulk containers	Mill irregularly shaped particles. Use mass flow bins to eliminate rathole flowing. Vent powder transfer tubes.

Agglomeration

Drug substances with sticky surfaces can agglomerate into larger particle sizes. The agglomeration can occur during the drug substance storage and in the process of drug product manufacturing. For the latter case, as the drug particles cascade and come into contact with one another, a snowballing effect produces agglomerated particles of the drug substance form. The inclusion of agglomerated particles in a single-dosage form could result in a superpotent dosage form.

Agglomerates can often be detected visually after the completion of blending operations. Passing the blend through a mill after the initial blend can reduce the impact that agglomerates have on content uniformity.

Blend and dosage forms with drug substance agglomerates may have high within-location variances, as only one of the

Potential sources of variability that can affect blend and content uniformity include incomplete mixing, segregation, raw material characteristics, agglomeration, and blend sampling bias.

replicate samples may contain them. Because superpotent tablets may not be commonly observed, and the impact of agglomeration can be diluted across the batch. The problem may go unnoticed, leading to the false conclusion that the batch quality is acceptable.

Blend Sampling Bias

Sampling bias can occur when blend samples are removed from mixers. Causes of sampling bias range from differences in the physical characteristics of the formulation components to poor sampling techniques or poor methods to determine sample size. If the sampling technique is not properly developed, the blend samples are likely to be nonrepresentative of the true uniformity of the blend, resulting in a "bad blend, but good drug product content uniformity" situation. When blend uniformity data are inconsistent among batches, even if there are no changes on material properties and process conditions, sampling bias may be the cause.

When blend sampling bias is present, the overall standard deviation is typically high (e.g., greater than approximately 4.5%), and most of the variation may be attributed to the within-location term. If the high blend within-location variance component is "real" (e.g., poor mixing on a unit dose scale), it will carry over to the dosage units, which will also have a high and dominant within-

location variance component. As a result, blend sampling bias would be ruled out and the blend is not uniform. If the overall standard deviation for the dosage forms is low (e.g., less than approximately 3%), and that variation is distributed evenly for the between-location and within-location components, blend sampling bias is likely.

ASSESSING BLEND AND CONTENT UNIFORMITY DATA

The primary purpose of blend uniformity analysis is to demonstrate that the drug is uniformly distributed throughout the blend, as reflected by the standard deviation of blend data. Although the mean for all samples is reported, the value is often off target due to sampling bias. For example, the preferential flow of excipients (and poorer flow of the drug substance) into the chamber of a sampling thief can result in a lower, albeit consistent mean. For this reason, the mean of dosage units tested (either in-process or during release testing) should be the only assay value of concern.

Blend and content uniformity should be assessed together. The assessment should include a thorough review of the data and information associated with the batch, as well as product history. Investigations for batches that are inconsistent with historical data should focus on events that may have occurred around the time of batch manufacture (e.g., a new lot of material, a change in the drug substance synthesis, different operators sampling the blend) that could incorporate variability into the process.

Data from each location should be plotted for both the blend and dosage units to assess the spread and any trends in the data [6]. A side-by-side comparison of the means, standard deviations, and variance components for the blend and dosage units should be conducted to determine whether the results are consistent. In general, if the standard deviation is less than approximately 3%, the blend and dosage forms can be considered uniform. Standard deviations greater than 3% may be subjected to VCA to identify potential areas for process improvement.

For the blend, a high between-location variance component implies that the blend is not uniform across all regions in the blender, signifying insufficient mixing on a macro scale. For tablets, a high between-location variance component implies that the dosage units are not uniform across the entire compression or filling process.

For both the blend and dosage units, high within-location variance components imply differences in the assay values for replicate samples within a single location. High within-location variance components can also be indicative of sampling bias.

CONCLUSION

VCA is a useful tool to identify root causes of blend and content uniformity issues, particularly during formulation and process development. Using statistically based sampling plans and proper sampling techniques ensures the proper data are collected to enable proper statistical analysis. Potential root causes can be investigated and mitigated, which could lead to process improvements.

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In memory of our colleague and friend, Anthony Carella.

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SHIFTS IN CONTAINER CLOSURE INTEGRITY TEST METHODS

By Oliver Stauffer and Juliet Mullan

Newer container closure integrity (CCI) test methods are more accurate and reliable than longtime industry standards. Transitioning to include deterministic testing alongside probabilistic methods may seem daunting at first, but it is in the industry's best interest.

Container closure integrity is determined by evaluating whether a given container maintains its sterile barrier. With the August 2016 revision of United States Pharmacopeia (USP) Chapter <1207>, "Package Integrity Evaluation—Sterile Products," the industry has begun to shift from probabilistic to deterministic CCI testing methods. Probabilistic methods generally require a series of stochastic, sequential events that are outside the operator's control. Deterministic test methods follow a predictable chain of events and use controlled test equipment to capture an objective measurement of leakage [1]. USP Chapter <1207> guides industry professionals on CCI testing, including available methods and which considerations are appropriate to evaluate when deploying a test method. The tests used to determine CCI have critical effects on product stability and patient safety, so it is vital to use the best method for a particular container in the interests of saving time and money and ensuring patient health [1].

When evaluating different leak-testing methods, it is important to understand that all packages leak to a certain degree. Maximum allowable leakage limits (MALL) are set for each package type and product configuration to provide a basic target for ensuring CCI. For parenteral product classes, defects in the single-micrometer range are considered critical [2].

PROBABILISTIC METHODS AND DETERMINISTIC ALTERNATIVES

Historically, probabilistic CCI test methods such as water bath, dye, and microbial ingress tests have been used to determine package quality. These tests are limited in their effectiveness and reliability for several reasons. Chief among them are the subjectivity of the results, the lack of standardization, and the lack of control a test operator has over certain stochastic elements of the test process. Also, these test methods lack industry standardization, with different sites using different chemistries, cycle times, and test parameters to achieve test results.


Oliver Stauffer

Most CCI test methods apply a condition to the test sample to then observe a response. In an ideal test method, little sample preparation would be required and method deviation would be reduced by limiting the steps involving operator intervention. The test conditions applied to the test sample should be measured and controlled. The final test method observation should not be subjective or variable; rather, it should be a measurement that can be traced back to certified, calibrated standards. Deterministic methods eliminate variability where possible and improve clarity with regard to the samples being tested.

Deterministic leak testing, such as vacuum decay, high-voltage leak detection (HVLD), or headspace analysis [3, 4], is based on phenomena that follow a predictable chain of events. Leakage is measured using physicochemical technologies that are readily controlled and monitored, yielding objective quantitative data [1]. Deterministic leak tests are performed on calibrated machines designed to control potential variables, perform uniformly under varying conditions, produce traceable test results quickly, and detect smaller leak sizes with greater reliability than probabilistic methods.

The critical nature of CCI tests and the implications they have for patient safety make accuracy of the test result paramount. While a probabilistic test may still be effective for certain applications, shifting to methods with greater reliability clearly has distinct value. Table 1 lists the factors that must be considered and provides questions to help determine which testing methodology to use based on common package/product combinations.

Table 1: Selecting a new testing methodology based on common package/product combinations.

Question	Oral Dose Tablet in Aluminum Cold Form (e.g., Thyroid Hormone)	Parenteral (Biologic Liquid-Filled Vial)
What characteristics are important to patient safety? How does the product achieve this?	Prevents oxidation of the product by maintaining barrier properties and package integrity.	Chemical stability of the product; product sterility (no microbial growth). Leaks in the single-digit-micron range pose risks; must ensure that the sterile barrier is maintained.
To what level should that package characteristic be challenged, commensurate with the level of acceptable risk associated with patient safety?	Oxidation level is contingent on the blister package's headspace and defect size (Fick's first law).	Down to the single-digit-micrometer range, in accordance with as many samples as can be reliably tested. Test an appropriate quantity down to the critical defect size to achieve statistically relevant assessment of the batch.
Critical Follow-up Questions		
• Is there a method to physically observe a specific leak characteristic? If so, what are the physicochemical interactions of the package/product combination when performing that method? • Are there any gaps in the method performance or reliability? How do physical and chemical principles support the detection of leaks? Are there probabilistic aspects of the method? • What controls are necessary to prevent probability from coming into play? What enhancements can improve the detection capability or reliability of that test method? • What is the most effective way to challenge the method and verify performance?		

Alternatives to the Bubble Emission Leak Test

The bubble emission leak test is described in USP Chapter <1207> as a probabilistic test to detect gas leaks in containers. The method involves submerging a container in water and applying a vacuum. Any bubbles streaming from the container indicate a leak. A variety of factors contribute to the probabilistic characterization of the bubble emission method [1, 5].

- The size of leak that can be detected depends on the water surface tension and the pressure differential between the water bath and the inside of the container.
- A stream of bubbles will only be generated when there is a pressure differential between the inside of the container and the outside.
- A flexible package will expand under the vacuum, reducing the pressure differential, which is needed to create a stream of bubbles.
- Pouches with varying shapes and volumes will achieve different differential pressures and will be more or less able to generate a stream of bubbles from the same size leak.
- Liquid may interact with hydrophilic container contents to plug a leak.
- The negative test pressure may be a gauge or absolute pressure level, which will have implications when performing the same test at different elevations.

An alternative to the bubble emission leak test would be a vacuum decay leak test that is deterministic. Ideal vacuum decay systems will draw an absolute vacuum (not gauge) on the container in a controlled test space and monitor the vacuum level for any fluctuation. For flexible packaging, a flexible membrane would be beneficial, compensating for shape and volume variations between samples. The vacuum decay measurements include the final pressure and the change in pressure in the test chamber during the test cycle, producing an accurate and traceable measurement of leakage for each test cycle. The vacuum decay test method outweighs the water bath in sensitivity, reliability, and overall test method reproducibility [1, 5].

Alternatives to Dye Ingress

The dye ingress method is similar to the water bath but requires a series of events to occur for a defect to be effectively detected. The method begins with submerging the container beneath a dye solution inside a vacuum vessel and drawing vacuum on the vessel. Next, in stage 2 of the test, a defective sample under the vacuum would need to leak contents into the dye solution. In stage 3, the vessel is brought back to atmospheric pressure, and the vacuum that had been developed inside the container in stage 2 would draw dye back into the container. The primary probabilistic challenges facing dye ingress are associated with stage 2 of the test cycle [4]:

- Enough volume needs to be evacuated from the container during stage 2 of the cycle to create sufficient vacuum inside the container to draw the dye into the container.
- If there is little to no air inside the container, little to no force will be generated in stage 2 to draw liquid from the container. In this circumstance, dye ingress in stage 3 is highly probabilistic.
- If there is air in the container, the chemical properties of the container contents will determine how effectively fluid contents can leak out of the container during stage 2. The vacuum applied in stage 2 will be less effective at drawing liquid from the container, especially with more viscous liquids.

The US Food and Drug Administration and the European Commission's Annex 1 require CCI testing to be performed with actual product or product mimicking the natural product physical and chemical conditions. Generally, there is little standardization for the dye ingress test, and the impact of container conditions on the method's performance further impedes the method's capability [4].

Two alternatives to the dye ingress method are vacuum decay and HVLD. The methods are vastly different in approach. Vacuum decay was described in the discussion of the bubble emission leak test as a deterministic test method. Under certain circumstances, specifically in testing proteinaceous aqueous solutions, vacuum decay may be less effective. With a vacuum-based test, proteinaceous or viscous contents can dry up within a container leak, sealing it off [4].

When testing a proteinaceous or viscous liquid, the better alternative would be to test using HVLD, which uses the principles of electrical capacitance to detect leaks in pharmaceutical containers. The technology can be calibrated and produces reliable and repeatable detection of defects under a wide range of product chemistries and container presentations. Method input factors are highly controlled and traceable to electrical standards.

EMBRACING THE SHIFT

Notably, each of the probabilistic test methods described in this article is a destructive test—the sample is adulterated upon completion. With less-expensive products, this may not be a particularly pressing concern. However, the ability to repeat an experiment is a cornerstone of good science, and CCI testing is increasingly becoming a science-based discipline. Destructive testing results are finite, and samples cannot be used for further analysis, regardless of the results.

Most deterministic methods are considered to be nondestructive, which means the tests can be repeated without damaging the sample in the process. Therefore, the test sample can be released into the supply chain after its integrity is confirmed. In instances

where a nondestructive method shows that the sample's CCI is compromised, the unadulterated sample can be inspected and analyzed further.

Shifting to a deterministic method for products in development requires that the physiochemical aspects of a product be evaluated to determine which test method is most appropriate. A third-party GMP lab can perform a full-scale test method development on the target product and provide significant guidance regarding the appropriate path forward. The test method developed by a GMP lab can be transferred directly to the manufacturing site.

Many in the industry are reluctant to embrace the shift from traditional probabilistic testing toward newer deterministic methods, and this is understandable. Transferring away from a probabilistic method for a product in production is often avoided because it involves significant effort for refiling. However, in the corrective-action period following a quality deviation, the rationale for shifting test methodology to a deterministic method becomes clearer.

The upfront costs of new test equipment is often a deterrent. But manufacturers should also consider how much value can be generated by deploying a reliable deterministic test method, as well as the costs that add up when using less-reliable probabilistic methods. If inaccurate information is impacting a successful batch release or obscuring stability data, there is a significant and real cost to that.

Deterministic test methods can provide quantitative results in a matter of seconds. Such quick results translate to quicker preventive actions, if necessary, without needing to discard large batches of product—saving time, money, and resources. Over a short period of time, deterministic technologies and the information they produce should provide significant returns on the investment.

Others may believe the traditional methods work adequately. However, having an acceptable status quo ought not be a reason to avoid updating best practices; the more options the industry has, the better CCI test methods can be tailored for each package/product combination. There is no single method that works for all package and product combinations, but sites operating with general product classes will often find a single suitable test method for that specific product class.

DEPLOYING NEW TEST METHODS

USP Chapter <1207> explains the importance of investigating the interaction between the package and the product when selecting a test method. Because the physics behind CCI tests are the foundation for the method's effectiveness, two criteria are paramount: vetting the physiochemical properties of the application and outlining the direct, practical nature of what the method measures.

Addressing the physicochemical nature of a CCI application requires asking many questions about the package and product combination. The product will often determine what sensitivity is required and which test method is optimal. What is the MALL, for example? If the product is parenteral, a risk assessment would show the need to challenge CCI to a high level of sensitivity to prevent microbial contamination. On the other hand, a radioisotope may be not affected by microbial ingress, but it may have a greater risk of product degradation from chemical contaminants. A lower-risk oral dose application may be relatively insensitive to environmental contaminants, but other, more sensitive ingredients may oxidize easily.

CONCLUSION

While some traditional methods have practical application in evaluating package quality, there is a clear case for evolving CCI determination to deterministic methods. For applications in which the test results have a high-stakes impact, there are aspects to each probabilistic method that preclude them from being considered over deterministic methods.

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About the authors

Oliver Stauffer received his bachelor of science degree from the University of Michigan and completed his MBA at Georgetown University. He began his career in analytical and research and development laboratories, with a focus on sensory technologies, physiochemical measurement, and test method development specific to package testing. Oliver joined PTI in 2005 as a member of the research and development team working on nondestructive testing of high-risk pharmaceutical packaging. In 2006, he joined the sales team as Applications Engineer for PTI Inspection Systems. He held the position of International Business Development Manager for PTI through 2010, followed by COO through 2015, focusing on global quality solutions for package inspection that provide the highest level of measurement accuracy and reliability. During his time with PTI, he has developed several technology platforms, measurement methodologies, and technology patents. He was appointed CEO of PTI in 2016 and has been a member of ISPE since 2013.

Juliet Mullan studied electrical and computer engineering at Carnegie Mellon University, then transferred to Queens College in New York City to pursue a degree in environmental science in an effort to contribute to discovering and implementing climate change solutions. She has been an avid reader, writer, and swimmer her entire life and looks forward to combining those passions to make the world a healthier, safer, and happier place. Currently, she is a swim instructor and lifeguard at a YMCA of Greater New York while she completes her degree.

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