PHARMACEUTICAL ENGINEERING®

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REGULATORY TRENDS & QUALITY INITIATIVES

Risk Management for Avoidance of Drug Shortages

An Evaluation of Postapproval CMC Change Timelines

Air Speed Qualification: At Working Position or Working Level?

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42 CONSIDERATIONS FOR A DECENTRALIZED MANUFACTURING PARADIGM

The biopharmaceutical industry must develop and implement innovative ways of working to be effective and efficient in the current healthcare ecosystem, in which high-quality medicines, adaptability, and assurance of supply are of critical importance. There are regulatory strategies and technologies emerging to address these challenges, but further progress must be made to fully harness the advantages of advanced and decentralized manufacturing techniques.

56 NEW EU AI REGULATION AND *GAMP® 5*

This article describes how *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* and related GAMP Good Practice Guides can be effectively applied to help meet the requirements of the proposed European Union (EU) artificial intelligence (AI) regulation for qualifying GxP-regulated systems employing AI and machine learning (ML).

62 ENABLING GLOBAL PHARMA INNOVATION: DELIVERING FOR PATIENTS

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DEPARTMENTS

HIGHLIGHTS - 2023 ISPE ASEPTIC CONFERENCE

ISPE

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By Michael L. Rutherford


Michael L. Rutherford

Regulatory, One ISPE, and New Leadership

Where has 2023 gone? The year is already three-quarters over. The ISPE 2023 Annual Meeting & Expo in Las Vegas, Nevada, is just a few weeks away. And I will be passing the gavel to Scott Billman, your next ISPE International Board Chair, at the Membership Luncheon on 16 October.

The Annual Meeting is the largest ISPE conference of the year, with extensive educational tracks, an amazing exposition hall with a wide range of vendors who support our industry, committee meetings, and one of the best opportunities to network and share knowledge with colleagues in your area of interest. If you have not yet registered for the Annual Meeting, please visit the conference website for more details and to register. It is surely going to be an event you don't want to miss.

PE THEME: REGULATORY

ISPE has had a long-standing relationship with regulatory agencies around the globe and has played a key role in defining and supporting pharma industry guidance in key technical and regulatory areas. So, the focus of this edition of PE should not be a surprise, especially with all of the activities and success in this area. ISPE's efforts on drug shortages have been ongoing for years and have resulted in new guidance on prevention readiness, released in May 2023, which addresses the evolving international landscape. Thanks to Diane Hustead for her leadership of this effort.

Five guides on Advancing Pharmaceutical Quality (APQ) have been published—Change Management (CM) System, Cultural Excellence, Corrective Action & Preventive Action (CAPA) System, Management Responsibilities & Review (MRR), and Process Performance & Product Quality Monitoring System (PPPQMS)—which furthers the potential for additional efforts in this critical area. ISPE also released a report on its work supporting the establishment of the European Health Emergency Preparedness and Response Authority (HERA), which is available at ISPE.org

The ISPE Harmonization Initiative, "Enabling Global Pharmaceutical Innovation: Delivering for Patients," led by Roger Nosal has been launched, with the objective to "catalyze consistent and harmonized interpretation and implementation of ICH guidelines" [1]. You can learn more about this initiative from the article on page 62. ISPE subject matter experts also participate in multiple regulatory-related initiatives in the US and EU, and ISPE has commented on five regulatory documents as of May. ISPE regulatory efforts are extensive—learn more about them in this edition.

STRATEGIC PLAN: ONE ISPE, AFFILIATES, AND CHAPTERS

When ISPE International launched the One ISPE program with the Affiliates and Chapters, the goals were to enable ISPE to successfully operate its worldwide business, achieve the ISPE vision and mission, provide an operating framework that fosters global growth, and enable synergistic value between ISPE International and the Affiliates and

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Chapters. As we work through our second year of the program, the success and benefits of the One ISPE program are being realized locally and globally.

I've had the opportunity as Board Chair to interact with and participate in regional Affiliate and Chapter events, including, most recently, the face-to-face North America/South America Affiliate Council (NASAAC) meeting in May in Philadelphia, Pennsylvania, US, hosted by the Delaware Valley Chapter as part of their annual Symposium & Exhibition, and the face-to-face Asia Pacific Advisory Council (APAC) meeting in June in Manila, Philippines, hosted by the Philippines Affiliate in conjunction with their 15th Anniversary Conference and Expo.

Both conferences and expositions were very well attended and provided an opportunity to demonstrate how well these Affiliates and Chapters are doing. The regional meetings also highlighted the great work all the Chapters and Affiliates are doing locally to benefit our ISPE members. International Board members, as part of their Affiliate and Chapter Board Liaison roles, and ISPE staff, have also participated in numerous local events around the globe, helping build a better alignment and synergy between the Affiliates and Chapters and ISPE International.

ISPE International and the Board of Directors continue to be committed to our support of One ISPE and the Affiliates and Chapters to foster growth on the global level. With the approval of the Southwest Chapter in May, we welcomed our 40th Affiliate/Chapter in the US. This new chapter will be our host for this year's Annual Meeting in Las Vegas and is very excited to establish and implement local events to support this new region.

LOOKING AHEAD

Thank you to all of the Affiliate and Chapter leadership and committee volunteers for all of your work and efforts to support the One ISPE program and make these local ISPE organizations successful and beneficial for our members. I look forward to seeing everyone at the ISPE Annual Meeting in Las Vegas and our transition to our 2023–2024 leadership at both the international and local level. Viva Las Vegas!

Reference

International Society for Pharmaceutical Engineering. "Enabling Global Pharmaceutical Innovation: Delivering for Patients." https://ispe.org/initiatives/regulatory/enabling-global-pharmaceutical-innovation-delivering-patients

Michael L. Rutherford is Executive Director, Computer Systems Quality and Data Integrity, at Syneos Health, and the 2022–2023 ISPE International Board Chair. He has been an ISPE member since 2003.

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By Vivien E. Santillan


Vivien E. Santillan

TRANSCENDING BOUNDARIES AND MAKING CONNECTIONS MATTER

For the past few months, ISPE Asia Pacific Affiliates and Chapters have been busy reconnecting with colleagues through in-person conferences. Collaboration, innovation, and technology are common themes; events also incorporated quality culture and excellence.

In these conferences, the Women in Pharma committee of each Asia Pacific Affiliate engages with students, Emerging Leaders, and industry members; attends quality programming for personal and professional growth; and engages in a platform that acts as a catalyst for community development.

ISPE SHANGHAI—LAUNCH OF WOMEN IN PHARMA

Shanghai ISPE Pharmaceutical Information Company (ISPE Shanghai) held its 2023 Global Biomedical & Pharmaceutical Engineering Forum & ISPE China Annual Conference 26–27 May in Hangzhou, China. The conference, led by ISPE Shanghai, focused on the latest regulatory guidelines and expectations from the United States Food and Drug Administration (FDA). The conference also highlighted ISPE Shanghai's Communities of Practice, with Women in Pharma launching through a networking activity.

As Co-Chair of Women in Pharma, I was given an opportunity to present Women in Pharma's mission and objective and to share how ISPE members can benefit from its programs. Tina Lan, Chair of the ISPE Shanghai Women in Pharma committee and a Computer System Validation (CSV) Consultant of PQE Group presented the plans of the committee, including the mentorship program. The WeChat group for ISPE members, who are interested in joining and supporting the mentorship program, was also officially launched.

INDONESIA AFFILIATE—BUILDING CONFIDENCE

The Indonesia Affiliate's conference was held 6–7 June with the theme of: Technology Innovation—Adhering to Ethical Behavior and Ensuring Patient Safety. A Women in Pharma exclusive luncheon was held on day 2. The event provided its Women in Pharma members with a venue to discuss personal growth, with a session on building confidence in the workplace. There was lively interaction and exchange of insights among 22 women. The event ended on a high note with inspiration and motivation for boosting one's self-confidence.

> We look forward to the ISPE community expanding and, more important, driving the mission and vision of Women in Pharma.

PHILIPPINES AFFILIATE—HIGHLIGHTING INFLUENTIAL WOMEN

This past June, the Philippines Affiliate celebrated its 15th anniversary, and what a celebration it was! Between 14–15 June, over 200 attendees gathered at the Conrad Manila for the ISPE Philippines Affiliate's 15th Anniversary Conference and Exhibition: Enabling Multi-Sectoral Collaboration Towards Innovation & Sustainability.

The excitement was evident as participants walked the expo hall and sat in sessions led by some of the region's most impressive thought leaders. The goal was to create a conference that highlighted the diversity within our region and the ISPE global community and provided equal opportunity for thought exchange. Several female plenary speakers and panelists led the conversations, including:

- Jesusa Joyce Cirunay, Director, FDA, Philippines
- Dr. Joey Gouws, Team Lead, Inspection Services, Prequalification Team, World Health Organization
- Janeen Wilkinson, Director, Global Quality, Regulatory Surveillance, Moderna
- Diane Hustead, Executive Director, Regulatory Affairs, Merck & Co.
- Rachelle Natividad, GMP Inspector Lead of the FDA, Philippines
- Dr. Imelda Peña, Director, Institute of Pharmaceutical Sciences, National Institutes of Health, Professor, College of Pharmacy, University of Philippines Manila

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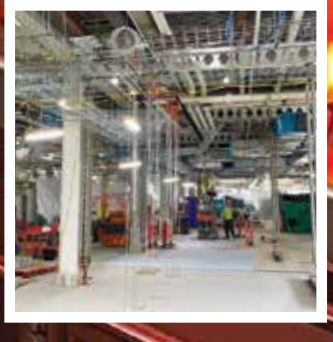

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In addition to ensuring diversity within our panels and presentations, a Women in Pharma event was held on Wednesday evening. Though the event followed a long day of educational sessions and networking, a packed room of more than 50 participants joined the session.

Pharmaceutical companies in the Philippines and most local Southeast Asia pharmaceutical companies are medium-sized, conservative, and family-owned organizations, which makes them culturally different from multinational corporations. This culturally driven mindset was the focal point of the conversation on how to communicate quality and compliance to senior management. Senior executives, a quality practitioner, and a consultant from the Philippines served as panelists. Colleagues from the ISPE Malaysia Affiliate, led by their Women in Pharma Chair, Mae Lee, and Affiliate President, Zarina Noordin, also joined the event.

COLLABORATE—MAKING CONNECTIONS MATTER

As the ISPE Affiliates and Chapters in Asia Pacific continue their journeys to pharmaceutical excellence, we look forward to the ISPE community expanding and, more important, driving the mission and vision of Women in Pharma. We will continue to work together to create a more inclusive industry where diversity of thought thrives.

Asia is distinct in culture, tradition, and language, but Women in Pharma has proven that despite this diversity there is a common agenda to drive excellence professionally and personally that creates impact and contributions to the industry as we shape the future of the pharmaceutical industry.

The 2023 ISPE Annual Meeting & Expo will take place in Las Vegas, Nevada, US, on 15–18 October. Women in Pharma will be hosting events throughout the week, and there will be plenty of opportunities to network and discuss how we can work together, collaborate, and move the mission of Women in Pharma forward. Join us and make connections that matter.

Vivien E. Santillan is Regional Director for Asia at Novatek International. She is Immediate Past President and Vice President of the ISPE Philippines Affiliate, Past Chair of the ISPE Asia Pacific Council, and Co-Chair of the Women in Pharma International Steering Committee. She has been an ISPE member since 2012.

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By Zen-Zen Yen


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CAREER DEVELOPMENT POWERED BY AI

The healthcare field is being transformed by artificial intelligence (AI) in remarkable ways, providing never-before-seen chances to enhance the well-being of patients. And the use of AI is transforming the job market and bringing numerwous benefits to both employees and employers.

Regulatory authorities such as the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have already established guidelines and frameworks to evaluate and regulate AI algorithms used in medical devices and diagnostics. Additionally, we can see that AI has already made a big impact on our everyday routines and jobs, and it's only becoming more significant.

WHERE IS THE ROBOT THAT'S TAKING MY JOB?

For a long time, the notion was that automation and AI would replace the tasks of numerous workers in fields such as manufacturing and logistics. We are now realizing this is not the case. To me, it is surprising that AI has first made tedious research or even design tasks obsolete. AI is now capable of not only rapid research and data collection, but also of creating music and images. As an Emerging Leader (EL) or student, you might wonder how AI can support you on your career path.

FINDING THE RIGHT FIT

AI-powered career development tools have made it easier to navigate the job market and find the right fit for your skills, interests, and personality. Researching roles and companies can be done via a single command within ChatGPT or Google Bard. These two AI tools can provide you with valuable insight into a role or company culture and you can program a scraper to do the job search for you.

Once you have identified potential job opportunities, AI tools can assist with crafting resumes and cover letters tailored to each position. Platforms such as Kickresume automate most of the tedious tasks involved in creating a compelling resume, allowing you to generate an impressive CV effortlessly by leveraging the data from your LinkedIn profile.

The use of AI is transforming the job market.

PREPARING FOR (TOUGH) CONVERSATIONS

AI tech is getting better and better, so students and ELs must keep up with the ever-changing digital landscape. Need a coach or someone to practice with for an interview? Communication coaches that analyze natural language can help potential applicants practice interviews using AI-powered simulations like Interview School, which has up-to-date interview questions and AI-assisted feedback. The use of communication coaches powered by AI can also enhance dialogue skills or offer guidance on how colleagues should adjust their communication approach according to their partners' preferences.

BOOST YOUR PERFORMANCE

A major component of several job positions involves investigating, putting information into context, and transforming it into ideas and plans. ChatGPT or Google Bard can accelerate the data mining process vastly. Analytics platforms like Tableau and SAS can visualize data more strategically, ultimately leading to better decision-making. Putting the data into a presentation may be a thing of the past thanks to tools like Gamma. For writing reports, there are tools like Grammarly or Hemingway Editor to help improve your tone, grammar, or flow.

A NEW FUTURE

The use of AI is transforming the job market in various ways and brings numerous benefits to both employees and employers. ELs and students can leverage AI-powered applications in their daily job in ubiquitous ways. Do you use AI regularly or want to share your tips and recommendations with me? I look forward to hearing from you!

Zen-Zen Yen is Head of Engineering for Bayer AG and the 2022–2023 ISPE International Emerging Leaders Chair. She has been an ISPE member since 2016.

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RISK MANAGEMENT FOR Avoidance of Drug Shortages

By Christine M. V. Moore, PhD, Jean François Duliere, John Groskoph, Diane Hustead, MS, and Christopher Potter, PhD

Shortages of essential medicines around the world have been an ongoing concern for patients, caregivers, and regulators and have been exacerbated by the COVID-19 pandemic. Many regulators have instituted requirements for reporting potential or actual drug shortages [1]. To further minimize drug shortages, regulators in the United States and France recently established requirements for risk management on drug shortages avoidance [2, 3]. Such requirements could spread beyond these two countries, especially because risk management for product availability is included in the revision of the ICH Q9(R1) guideline "Quality Risk Management" [4].

To support development of the revision and rollout of ICH Q9(R1), ISPE formed teams to compile comments on the ICH Q9(R1) draft guideline and to prepare examples for potential inclusion in ICH training material. Presented here is a summary of the work from members of the ISPE team on risk management for drug shortage avoidance, initiated for potential inclusion in International Council for Harmonisation (ICH) training material. The team members who developed this approach came from diverse organizations, backgrounds, and expertise—not unlike a well-designed risk assessment team.

The application of formal risk management activities for drug shortage avoidance has historically been an internal industry business practice, with few published examples or clear industry standards. This article presents a general approach for assessing and mitigating the risk of drug shortages through a product's supply chain and over the product's lifecycle.

The approach is expected to be applicable over all pharmaceutical modalities (e.g., small molecules, biologics, cell and gene therapies), all stages of manufacturing (e.g., drug substance, drug product, packaging), and over the lifecycle of the product. It can be considered part of business continuity planning, as related to drug shortage prevention [5].

Furthermore, the ISPE team believes that the approach presented here is consistent with recent expectations for risk management plans (RMPs) by the US Food and Drug Administration (FDA) [6] and for shortage management plans (i.e., plan de gestion des pénuries - PGP) by France's National Agency for Medicines and Health Products Safety (ANSM) [7]. The approach presented here is intended to be an example and is not the only way to address risk management for drug shortage avoidance.

OVERVIEW OF THE RISK MANAGEMENT APPROACH

The approach developed by the ISPE team to address risk management for drug shortage avoidance follows the general approach outlined in ICH Q9(R1) and is summarized in Figure 1. As described in ICH Q9(R1), considerations in risk management should include the appropriate level of formality and manage and minimize subjectivity.

- Initiate quality risk management process: Initiation of a quality risk management process begins with evaluation of the priority of products to inform the appropriate level of risk management. The evaluation of priority can include factors such as importance to the patient from a therapeutic perspective, regulatory requirements, and business significance. The scope of the evaluation can cover the entire supply chain for a product or be limited (e.g., single manufacturing site).
- Risk assessment: For each product labeled as a priority, a risk assessment is conducted: hazards are identified, potential risks are analyzed using the likelihood and potential impact of the hazards, and all are evaluated against predetermined criteria. Risks to supply continuity are addressed by identifying product/process and business/operational hazards and analyzing those hazards

over the manufacturing operations and for the manufacturing materials and components. In the approach presented here, the potential hazards are considered using a generic approach that is applied to segments, or nodes, of the manufacturing process.

- Risk control: Following the assessment of risk, risk controls are established and are the output/results of the quality risk management process. Mitigation plans with preventive measures are developed and implemented as a part of business continuity planning to reduce the risk of supply disruptions [5]. Preventive measures could include proactive or on-demand interventions. Because risk is never zero, there is a need for risk acceptance of residual risk after the mitigation efforts. Generally, there is a lower risk acceptance tolerance for higher-priority products.
- Risk communication: Risk communication occurs throughout the risk management process, including internal communication of the findings from the assessments and controls and external communication with health authorities, as appropriate. The risk management process helps provide a structured approach that enables more effective communications.
- Risk review: Over the lifecycle of the product, risks and preventive measures should be reevaluated on a periodic or event driven basis, with the risk assessment and risk controls being updated, as appropriate.

The next sections offer more detail on the individual steps of the risk management approach for drug shortage avoidance.

STEPS OF THE RISK MANAGEMENT APPROACH

Initiate Quality Risk Management Process

Determination of products for risk assessment

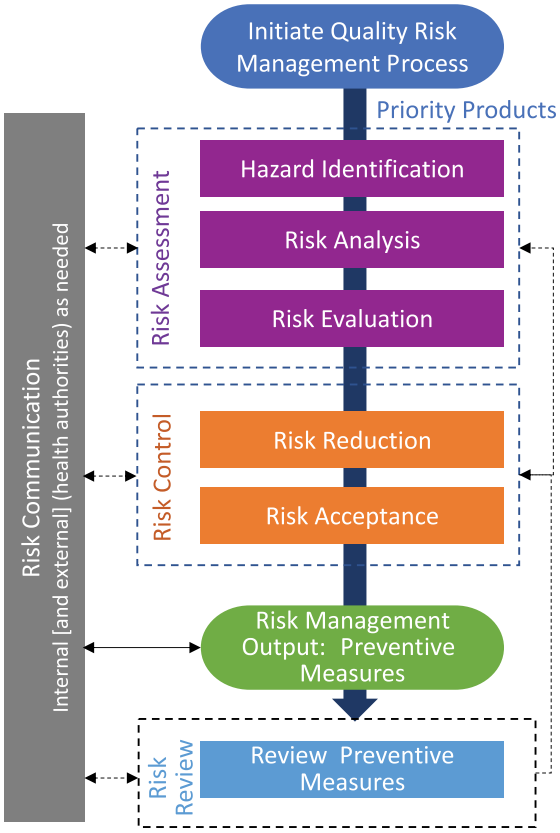
Not all products have the same magnitude of impact when they become unavailable or have the same susceptibility to significant supply disruption. Accordingly, the appropriate level of risk management is optimally established based on the therapeutic importance of the product, related regulatory expectations, and potential business and operational considerations.

Prioritization for risk management activities ensures the most significant products have optimal supply resiliency support and that correlating investments are sustainable. Priority of individual products should be assessed periodically because clinical, regulatory, and business and operational perspectives will change over their lifecycle and the changes may not have a consistent trajectory.

Considerations for product prioritization include, but may not be limited to:

- Therapeutic importance: patient population, indication, dosage form, alternative therapy, generic availability, emergency use, product seasonality
- Regulatory requirements: part of a national stockpile, on a governmental prioritization list
- Business/operational considerations: market share, revenue position, failure-to-supply agreements, operational interconnections to other products, time/complexity to manufacture resupply

Figure 1: Approach to risk management for drug shortage prevention, based on ICH Q9 concepts.



This prioritization exercise should include individuals with the appropriate knowledge, such as those in medical, regulatory affairs, supply chain, and marketing.

Many products cannot clearly be designated high priority or low priority. In such cases, the relative priority of the product should guide the decision process for the appropriate levels or layers of risk reduction to be applied. Discretionary risk management activities may always be applied to lower-priority products to ensure greater reliability and supply resiliency across the portfolio.

Determination of sites and markets for risk assessment

Pharmaceutical supply chains typically are highly complex; that complexity can make the task of an end-to-end risk assessment for drug availability seem overwhelming. A risk assessment can be conducted for only a portion of the supply chain (e.g., for a single facility or destination market), although an end-to-end assessment can provide a more holistic overview of potential risks and reveal interdependencies. To help structure the risk assessment approach, the ISPE team recommends characterizing the supply chain using manufacturing nodes for the assessment.

Figure 2: Illustration of the nodes analyzed in an assessment of risks for product availability.

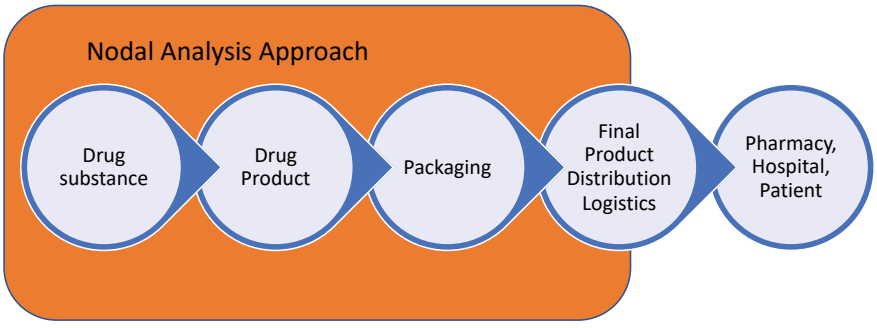
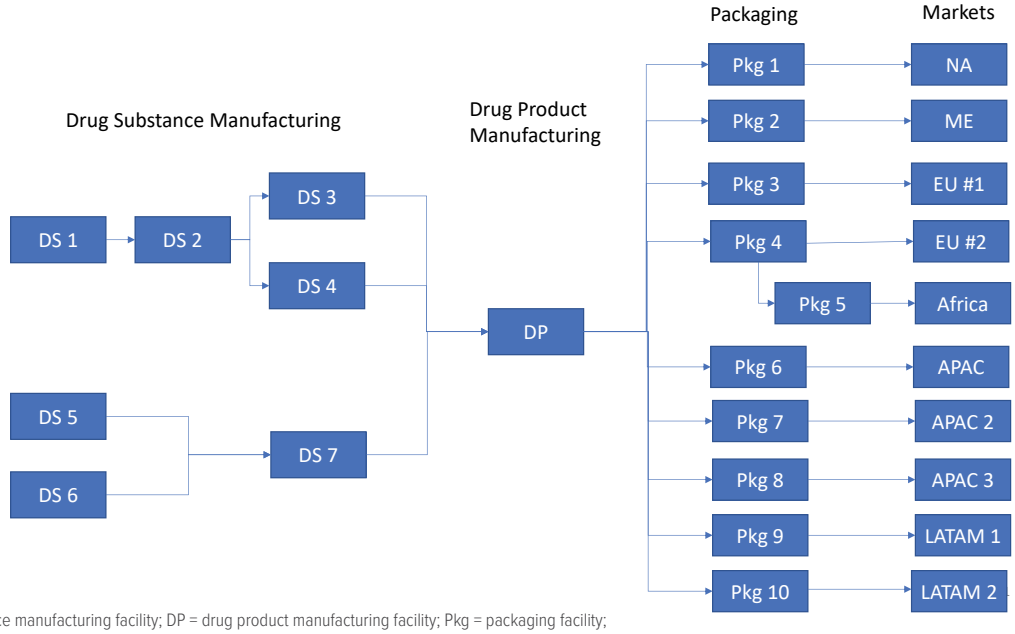


Figure 3: Example of a pharmaceutical supply chain.



(DS = drug substance manufacturing facility; DP = drug product manufacturing facility; Pkg = packaging facility; Markets = North America (NA), Middle East (ME), Europe (EU), Asia Pacific (APAC), Latin America (LATAM))

Typical pharmaceutical manufacturing steps include drug substance, drug product, and packaging, illustrated as nodes in Figure 2. For the purposes of the risk assessments in this approach, a node is inclusive of transportation from the end of the previous manufacturing step to the current step. Although the product is ultimately distributed to the patient, pharmacy, or hospital, the control of product by the pharmaceutical manufacturer usually ends at transfer of the product to a distributor. Transportation from the packaging site to the distributor is included as a non-manufacturing node called "final product distribution logistics" in Figure 2.

Actual pharmaceutical supply chains are much more complex than the linear description in Figure 2. A hypothetical example of a typical pharmaceutical supply chain for a major product is shown in Figure 3. Because each manufacturing location can have unique risks, the ISPE team recommends that each manufacturing site be considered a separate node in the risk analysis. It may be possible to use a common risk assessment for similar products or the same manufacturing sites. For example, drug products with similar storage conditions that have a common site, materials, and equipment for packaging will likely have identical risks at the packaging node.

When multiple manufacturers contribute to the drug's supply chain, an important consideration for regulatory compliance is which manufacturers need to perform risk assessments. US law requires manufacturers of covered drug products and

manufacturers of associated active pharmaceutical ingredients (APIs) to establish "redundancy risk management plans" [2]. Covered drug products are considered those that are life-supporting or life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition (including those used in emergency medical care or during surgery), or those that are critical to the public health during a public health emergency. The associated FDA draft guidance for risk assessments [6] defines different levels of stakeholders (i.e., primary, secondary, other) and explains that primary and secondary stakeholders are required to prepare RMPs for covered products.

In France, the expectation is that drug product manufacturers prepare a shortage management plan (PGP) for designated products [7], including evaluation of drug substance, drug products, and critical components. Designated products are defined as drugs or classes of drugs of major therapeutic interest (MITMs) for which interruption of treatment is likely to endanger the prognosis of patients in the short or medium term, and/or increase the severity or potential progression of disease.

Good communication between manufacturing sites is essential in effective risk management, regardless of who prepares the risk assessments at each node. Although the FDA draft guidance calls for the primary stakeholder (e.g., application holder) to communicate as much of their risk assessment as possible with secondary stakeholders, the ISPE Q9(R1) team believes that two-way communication is essential.

To determine their regulatory obligations, contract manufacturing organizations (CMOs) of drug substances need to know from the drug product manufacturers how their drug substances are used. Similarly, drug product manufacturers need to understand the manufacturing risks from their drug substance CMOs. Two-way communication between CMOs and their clients can lead to holistic and comprehensive risk management approaches.

Prepare for the risk management process

Good preparation is essential for a meaningful and fair risk assessment. Before starting any risk assessment exercise, a clear problem statement or risk question should be posed; for example, "For this particular manufacturing site, what potential hazards might have a significant impact on the availability of a drug substance?" Additionally, the assumptions and constraints should be identified; for example, if the assessment will include the risks from steps managed under CMOs.

Next, the level of formality should be determined, which will inform the amount of detail and documentation associated with the risk assessment. Typically, the degree of formality is commensurate with the criticality of the matter being addressed. Assessment tools with clear definitions of risk levels should be chosen, then aligned with the level of formality.

Examples of assessment tools for quality risk management are provided in Annex I of ICH Q9(R1) [4]. Finally, the individual or team designated as the approver, or decision-maker, of the risk management activity should be determined prior to starting the risk assessment process.

The risk assessment team should be cross-disciplinary, diverse, and include subject matter experts (SMEs) from a broad array of functions throughout the organization, such as manufacturing, medical affairs, procurement, quality, regulatory affairs, sales and marketing, supply chain, technical and manufacturing operations, customer relations, external business partnerships, and legal [5].

The setting for risk assessments should facilitate continuity of information flow, such as in-person meetings or appropriate online tools (e.g., electronic whiteboards). Ideally, the risk assessment team should be led by a skilled facilitator who understands the technical content of the discussion but can remain neutral. It also can be beneficial to have an objective observer from outside the team to provide an independent voice and challenge assumptions. Use of a skilled facilitator and an objective observer can help reduce subjectivity.

Subjectivity can lead to decision-making based on individual biases and opinions rather than the collective facts and data. The strategies discussed in this section can help reduce subjectivity, but it can never be eliminated. Training can help the risk assessment participants identify and minimize subjectivity. Finally, the decision-maker or approver of a risk assessment should ensure that subjectivity is appropriately managed.

Figure 4: Example of an Ishikawa diagram to identify potential hazards to product availability.

Review of the RMPs for drug shortage avoidance should occur both on a periodic and event-driven basis.

Risk Assessment

Hazard identification

For the analysis at each node, the ISPE team employed an approach commonly used to address quality issues called an Ishikawa diagram (also called a cause-and-effect or fishbone diagram) [8], shown in Figure 4. The hazard is defined as supply disruption leading to the patient not receiving their medication, which can, in turn, lead to patient harm, such as disease progression or life-threatening situations. This Ishikawa diagram lists potential hazards (i.e., the causes) that could lead to supply interruption (i.e., the effect). The factors in Figure 4 are grouped into categories of potential causes represented by lines leading into the spine. The categories include traditional ones (i.e., material, method, measurement, machine) and some that were added or modified for this specific purpose (i.e., management, major event, market).

Figure 4 is a generic diagram, intended to be used as a starting point for the hazard identification step of a risk assessment for drug shortage avoidance. Not all potential hazards will be applicable to all products, and additional hazards may apply. Furthermore, many other risk assessment tools other than the Ishikawa diagram can be used for assessment of hazards to drug availability, like a preliminary hazard analysis.

Risk analysis

The Ishikawa diagram in Figure 4 can be used as a risk assessment tool and starting point for the risk analysis. Using a group of knowledgeable SMEs in an environment to minimize subjectivity, this assessment tool can be applied at each node of the manufacturing process to identify which potential hazards are most likely to cause a supply disruption, based on the likelihood of occurrence of the hazard.

The ISPE team does not recommend a detailed spreadsheet be made that includes every potential hazard at each node and justification as to why each hazard was or was not relevant. Such efforts could be overwhelming and add little value to the process considering the complexity of pharmaceutical supply chains. Rather, it is recommended to focus on the hazards that are most likely to lead to supply interruption.

Risk analyses often include a quantitative calculation of the likelihood of occurrence of the hazard and the significance of its effect. However, such a calculation for drug shortages can be challenging because there are numerous factors involved in any potential hazard that can affect the extent or duration of the supply disruption, and its subsequent impact for patients. Consequently, it may be beneficial to use more qualitative ratings (e.g., high, moderate, low) to categorize the potential impact of the identified hazards. Examples of scenarios and their associated ratings based on past experience can help provide consistency between the risk assessments performed for different products or by different teams.

Risk evaluation

The quantitative risk score or qualitative risk rankings are compared against predetermined criteria to make decisions. The threshold for applying risk reductions could be dependent upon the risk priority, as part of the business continuity plan [5]. Lower-priority products can tolerate a higher level of risk before triggering risk reduction activities.

Table 1: Simplified example of risk evaluation for a drug product aseptic filling operation.

Potential Hazard	Details	Inherent Risk Level (Before Mitigations)	Current Mitigations	Risk Level (With Current Mitigations)	Potential Additional Mitigations
Disruption of API supply	• Recent adverse compliance signals at one API source • Multiple API sources qualified but not filed in all markets	High	Supplier oversight through audits on a risk-based frequency	Moderate	• Work with API supplier to improve compliance posture • Explore new API suppliers • File second source in all markets as a backup
Disruption of container closure components	• Single source of vial cap with long lead time	Moderate	Stockpiling of vial caps	Low	• Increase stockpiling of vial caps to provide a buffer • File PACMPs to allow for fast change of vial cap, if needed
Loss of sterility in drug product	• Complex manufacturing (aseptic filling)	Moderate	• Engineering controls • Ongoing environmental monitoring • Preventative maintenance and process trending	Low	No additional mitigations needed

Low = unlikely failure
Moderate = possible failure
High = actual or likely failure

Existing mitigations are considered part of the risk evaluation: for example, stockpiling, manufacturing redundancy, and reserve capacity. The expected time needed to recover from a potential hazard leading to a supply disruption should also be considered as part of the risk evaluation.

An example output from a simplified risk evaluation for an aseptic filling operation is presented in Table 1. Only the potential hazards that have a moderate or high inherent level of risk are included. A risk level is determined based on current mitigations, such as stockpiling or alternate sources. If a moderate or high level of risk exists after current mitigations, further mitigations could be merited, as discussed in the following section.

Risk Control

Risk reduction

Robust risk reduction of potential drug shortages is most successfully achieved with layers of preparedness, including the organizational, operational, and product-specific levels over multiple areas of pharmaceutical manufacturing, as described in the ISPE Drug Shortages Prevention Model [9].

Organizational- and operational-level risk reduction activities are typically expansive, multidisciplinary undertakings that cut across products and operations. For example, organizational aspects could include investment in workforce capability and quality culture, whereas operational aspects could include supply, demand, and quality monitoring systems with early warning capability for rapid identification of disruptive events.

Figure 5: The ISPE Drug Shortages Prevention Model, including the 12 performance domains in the areas of quality and manufacturing maturity, regulatory, and technology and innovation.

Risk management for avoidance of drug shortage is increasingly a regulatory expectation, as evidenced by recent laws in the US and France and the inclusion of this topic in ICH Q9(R1).

ISPE has several programs and initiatives that can help assure continued supply of quality product and contribute to organizational and operational preparedness, including:

- ISPE Drug Shortages Prevention Model [9]
- ISPE Advancing Pharmaceutical Quality, which is a comprehensive program for assessing and improving an organization's quality management maturity, including guides on Change Management System [12], Corrective Action and Preventive Action (CAPA) System [10], Management Responsibilities and Management Review [11], Process Performance and Product Quality Monitoring System [13], and Cultural Excellence [14]
- ISPE Pharma 4.0™, which enables organizations to leverage the full potential of digitalization to provide faster innovations for the benefit of patients [15]
- ISPE Product Quality Lifecycle Implementation (PQLI®), which works at the nexus of pharmaceutical manufacturing and regulation to bring forward solutions that help advance new regulatory and technology approaches [16]

Product-specific risk reduction plans rely on the general organizational- and operational-level risk reduction measures. Proactive product-specific interventions and/or on-demand interventions can be applied to minimize disruptive events, as described next.

Proactive product-specific interventions:

- Early alert system: Embedded data collection and analysis to rapidly identify and facilitate response to potential or actual supply disruptions
- Stockpiling: Reserve stores of critical components and drug substances for further processing and/or reserves of finished drug product that could provide coverage for an extended period
- Safety stock: Term often used to describe an inventory buffer of drug product (i.e., shorter-term stockpiling)
- Flexible manufacturing: Manufacturing technology that allows for faster relocation (e.g., transportable modular manufacturing units) or rapid increase in scale (e.g., continuous manufacturing)
- Manufacturing diversity or redundancy: Increased assurance of supply continuity through a strategic geographical supply chain footprint, appropriate CMO alliances, and/or backup manufacturing lines and/or manufacturing sites, that ideally can be used with minimal or no regulatory impact
- Reserve capacity: Unused equipment time or operational shifts that can be expanded, typically with minimal to no regulatory impact
- Regulatory preparedness: Preagreement with regulators (e.g., postapproval change management protocol [PACMP]) to accelerate chemistry, manufacturing, and controls (CMC) filings for anticipated regulatory changes, such as for increased manufacturing scale or batch size or alternative manufacturing sites

On-demand product-specific interventions (often requiring regulator cooperation):

- Real location: Movement of materials from one market to another to compensate for a surge in demand (e.g., from a localized endemic)—if executed for product already manufactured; this approach may need agreement from regulators if the product appearance or label is not the same between markets
- Substitution: Alternate strength of the same product, which could be coupled with reallocation—requires discussion with regulators and possible communication with health care providers and patients
- Other regulatory assistance: Event-specific response—facilitated by early and transparent communication with the relevant health authority for event-specific responses such as import/export facilitation, regulatory discretion, accelerated reviews, or inspections [17, 18]

In general, manufacturers should use the proactive product-specific interventions listed previously to ensure supply resiliency and reduce the likelihood of drug shortages. The extent to which the proactive product-specific interventions should be applied is dependent upon complex factors, considering patient needs, regulatory requirements, and business and operational considerations.

For critical medicines in urgent health conditions, such as endemic or pandemic situations, government agencies may also conduct their own stockpiling efforts. Although regulators are often able to make exceptions for urgent situations, the on-demand regulatory interventions listed previously should only be considered as a last resort for unplanned events.

The FDA draft guideline for RMPs recommends that manufacturers include plans to repair the supply chain after a disruption [6]. Although anticipating all potential supply disruption scenarios is not possible, it can be useful to pre-plan multiple product-specific mitigation pathways and to understand their timelines and the efforts required for implementation. Simulated supply disruptive event exercises can help inform where risk reduction efforts may need to be adjusted. Ultimately, the product-specific mitigation pathways chosen during a supply disruption will depend on the specific circumstances.

Risk acceptance

Because some level of risk is always present, risk acceptance is an essential step of any risk management process. The designated approver of the risk management activity should understand and agree on residual risk. Generally, the priority of the product will guide the appropriate level of risk acceptance. While it is not typically required to document the residual risks, doing so can be helpful for future risk review efforts.

Risk Communication

Risk communication related to product availability should occur in multiple directions. Internally, it is important for all stakeholders (i.e., development, manufacturing, supply chain, compliance, regulatory) to understand the potential risks to product supply, know the mitigation plan, and align on acceptance of residual risks. Externally, suppliers and CMOs may need to be apprised of how their decisions can impact availability of finished products to patients.

The FDA draft guideline recommends that manufacturers of the final drug product share as much of their RMPs as possible with their CMOs. The ISPE Q9(R1) team believes that this information sharing should be reciprocal to facilitate coordinated risk mitigation plans for drug shortage avoidance. For example, preparation for potential increase in drug substance supply could be achieved through redundant capacity at a current CMO, by addition of an additional CMO or in-house manufacturing site, or by increased stockpiling.

Many health authorities have requirements for reporting actual or potential drug shortages [1]. It is best to be transparent and early when discussing drug shortage issues with regulators and to have detailed information about the timing and magnitude of the shortage, ideas for mitigating the shortage, communication plans to health care providers and/or patients, and to share any ongoing actions [9, 18]. Although health authorities can optionally use enforcement discretion or regulatory flexibility to help mitigate shortages, it is the manufacturer's responsibility to assure availability of product; they should not rely on regulators' actions to resolve or avoid shortage issues.

In the past, communication of risks and mitigations related to drug supply have typically only occurred during a shortage or near-miss event. These communications will likely happen more frequently in the future, based on recent guidelines and the inclusion of the topic in ICH Q9(R1) [4]. For example, the French law requires communication of a manufacturer's PGP on a yearly basis; FDA can review RMPs upon inspection [6, 7].

Risk Review

Review of the RMPs for drug shortage avoidance should occur both on a periodic and event-driven basis. The ISPE Q9(R1) team supports a risk-based approach for determining the frequency of the risk review, considering priority factors such as patient needs, regulatory requirements, and business and operational considerations. Events that could trigger a reassessment and revision of the RMP for drug availability include but may not be limited to an actual shortage or near-miss event, change in supplier, unfavorable internal audit or health authority inspection, natural disasters, and geopolitical events.

As shown in Figure 1, risk review could lead to a modification of the risk assessment or risk control steps. The information generated during the risk management activities includes important knowledge that can be useful for future decision-making and to support the risk review process. Knowledge management and quality risk management work together as enablers of the pharmaceutical quality system, as described in ICH Q10 [19].

CONCLUSION

Risk management for avoidance of drug shortage is increasingly a regulatory expectation, as evidenced by recent laws in the US and France and the inclusion of this topic in ICH Q9(R1). In this article, the ISPE Q9(R1) team provided a comprehensive approach for analysis of risks to drug availability across the supply chain and over a product's lifecycle, using ICH Q9(R1) approaches. The approaches outlined in this article are expected to be appropriate to address recent regulatory expectations. Regardless of the regulatory requirement, understanding and mitigating vulnerabilities in supply chains is important for the pharmaceutical industry and ultimately for patients worldwide.

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AN EVALUATION OF Postapproval CMC Change Timelines

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As the demand for accelerated access to medicines expands globally, the pharmaceutical industry is increasingly submitting regulatory applications in multiple countries simultaneously. As a result, Boards of Health (BoHs) are challenged with approving these applications in an accelerated timeframe and accommodating the submission of postapproval chemistry, manufacturing, and controls (CMC) changes that pharmaceutical manufacturers submit after implementing improvements or optimizations.

Among global BoHs, variability in regulatory requirements and approval times for postapproval CMC changes has created an inordinately long delay between the first and last approval for a single CMC change for a pharmaceutical product. These long global approval timelines complicate supply chain management by delaying innovations that improve quality assurance and by increasing the potential for supply interruptions and shortages that impact patient access to products.

In this article, we describe the assessment of lag time for global regulatory approvals of postapproval CMC changes for multiple products over a three-year period. This approach incorporates all factors that influence the time for BoH approval as experienced in real-world situations and is relatively straightforward to calculate. It also allows for comparisons between companies and across different periods of time.

"In scope" were changes that required the most detailed BoH assessment in an impacted country (either by a notification or prior approval). For each country, the time required to achieve 90% probability of approval for a change represents the time between the first approval and each subsequent country BoH's approval for that change. We believe this represents the most relevant measure to assess the duration and impact on implementation and reflects the largest degree of complexity faced by industry to support postapproval CMC changes.

The results show that the time to achieve a 90% probability of approval for that change is ≥ 24 months in 63% of countries studied and ≥ 36 months in 15% of countries studied. In addition to delaying optimization of manufacturing and controls, these types of long delays for approvals discourage continuous process improvements for approved products.

We hope the results from this assessment stimulate adoption of the World Health Organization (WHO) Good Regulatory Practice (GRP) as well as implementation of International Council for Harmonisation (ICH) guidance that would improve the quality assurance of medicines for patients, decrease wait times with regulatory authorities, and reduce complexity and costs for industry.

VARIABILITY OF BOH APPROVALS

The time it takes to achieve global regulatory BoH approvals of postapproval CMC changes varies considerably around the world. The assessment of how long it takes to achieve global approval for postapproval CMC changes provides compelling data to improve regulatory processes, as the expedited implementation of optimizations for manufacturing and control of products increases quality assurance for patients globally.

The WHO is driving implementation by BoHs of GRP, which will improve regulatory processes [1]. The risk of a change to patients is inherent to the change itself, not in which country it is being reviewed. On this basis, it seems appropriate that there should be greater global consistency in the regulatory processes, data requirements, and BoH assessment durations required to establish the suitability of a change.

Previous publications on this subject provide general information on BoH assessment timelines (e.g., > 24 months) [2, 3]. The

assessment described herein includes recent "real world" data to describe the increasing probability of approval over time after the first global approval for a particular change. Taking Kuwait as an example (using data in Table 2), after the first approval for a change (anywhere in the world), there is a 50% chance of approval of that change in Kuwait within 24 months and a 90% chance of approval within 43 months.

Postapproval CMC changes have several drivers. For example, a site of drug substance or drug product manufacture may be moved and/or added to effectively manage product inventory and ensure supply chain reliability; a manufacturing process may be modified to introduce innovation or efficiency; or it may be necessary to modify the drug substance or drug product specifications during the life cycle of a product to accommodate changes in regulatory standards or expectations.

For each BoH, the time for approval of a change is influenced by the local regulatory framework, i.e., statutory requirements, regulatory guidance and prioritizations, data standards and requirements, BoH assessment criteria, and resource capacity. Considering regulatory frameworks, many BoHs, such as the United States (US), European Union (EU), United Kingdom (UK), Japan, and Canada, have filing categories (i.e., do and tell; tell, wait, and do; and prior approval) that are aligned with the potential risk to critical quality attributes associated with safety, efficacy, and quality of the product.

Pfizer regulatory teams local to the impacted countries have reported that in some countries, the marketing application authorization (MAA) of a drug is granted based on a specific supply chain and that the introduction of an alternate source of supply after approval requires the submission of a new MAA (e.g., Bolivia, Hong Kong, Malaysia, Philippines, and Vietnam). In these countries, a secondary packaging site change or an active pharmaceutical ingredient (API) manufacturing site addition triggers a new submission equivalent to that required for approval of a generic drug or a line extension, whereas these site changes may be filed as a notification in the US and EU.

Additionally, Pfizer regulatory teams local to the impacted countries have reported that some rest of the world (ROW) countries require prior approval from a country that is also dependent upon prior approval in a third country. For example, Russia can require a sample at submission (based on approval from EU or other country). Subsequently, Armenia requires prior approval from Russia before the submission can be made in Armenia.

This sequence of submissions and approvals can significantly extend the time to final regulatory approval and is not in proportion to the risk of the change to patients. The WHO GRP contains the concept of mutual reliance and recognition, meaning that one or more countries can accept the assessment outcome from a reference country. Such reliance would reduce the time to approval in some countries and avoid the need for repeat assessment of a change that may have been reviewed, approved, and already be in distribution to patients in the first approving countries.

Long global approval timelines complicate supply chain management by delaying innovations that improve quality assurance and by increasing the potential for supply interruptions and shortages that impact patient access to products.

The BoHs listed previously have well-defined data requirements; however, in the ROW, many countries have additional data requirements for the submission of a change. Due to the differences in the data (e.g., duration of stability data at time of submission) required by a BoH to support a postapproval CMC change, submission dates can vary by months or years between the first and last countries, due, in part, to the need to wait for additional and extraneous data. The ICH develops guidance for harmonization of data requirements for a postapproval CMC change [4]. However, these guidelines are not always interpreted or implemented consistently by country BoHs [5].

Increasing the capacity of a BoH, through implementation of WHO GRP and Good Reliance Practice, is a strategic focus of the WHO and the International Pharmaceuticals Regulators Forum [1, 6]. This implementation is designed to benefit all activities undertaken by the BoH, including the review of postapproval CMC changes, thereby optimizing BoH assessment times.

Improved alignment of regulatory processes will undoubtedly increase implementation of manufacturing optimizations, reduce the potential for drug shortages, lower the costs associated with managing inventory complexity, and encourage continuous improvement to increase quality assurance, particularly for approved older products [2, 3].

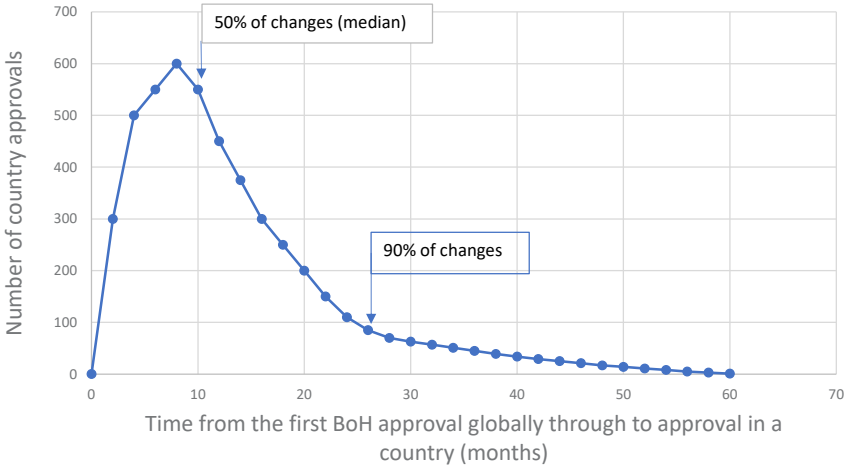
METHODS

The total time to approval of a global postapproval CMC change was measured, using data from Pfizer's GMP systems, as the time between approval in the first country to approval in each of the other countries impacted by that change. Table 1 shows a hypothetical example of how the assessment was performed. For each change, the time from first approval to approval in country A was recorded. Similarly, the time from first approval to approval in country B was recorded, and so on for all countries (represented by N) affected by the change. Then the durations were compiled for analysis and presented in the table.

Table 1: Hypothetical example of how an assessment was performed.

Change Number	First Approval for the Change Anywhere in the World	Approval in Country A	Duration from the First Approval of a Change to Approval for that Change in Country A (months)	Approval in Country B	Duration from the First Approval of a Change to Approval for that Change in Country B (months)
1	1 Feb 2017	1 Feb 2018	12	1 Feb 2020	36
2	1 Jun 2019	28 Nov 2019	6	23 Nov 2019	18
3	1 Sep 2019	30 Nov 2019	3	28 May 2020	9
N	1 Mar 2020	29 Jun 2020	4	24 Dec 2020	10
	Time after the first approval for a change, giving a 50% chance of approval in country A		5	Time giving a 50% chance of approval in country B	14
	Time giving a 90% of chance of approval in country A		10	Time giving a 90% of chance of approval in country B	31

Figure 1: Example of a skewed distribution.



For each country, only those changes with the highest assessment impact were included (e.g., Type II in the EU or a Prior Approval Supplement [PAS] in the US), as these would represent the greatest level of complexity for manufacturing and supply operations. In many countries, a prior approval category was required, but in other countries a notification of the same change was acceptable. BoH approval was based on either evidence of submission for a notification to a BoH or a BoH approval letter.

Scope

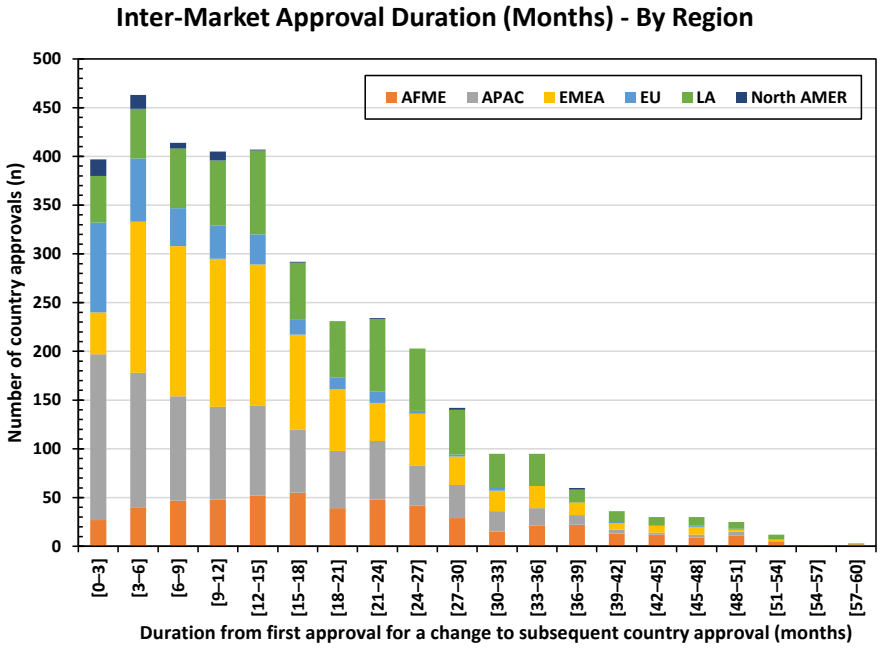
The scope of the assessment was for country approvals received in the calendar years 2018–2020. The first global approval for a change covered by one of these country approvals could have been received before 2018 and was needed for the calculations. On this basis, country approvals covering 2016–2020 were included in the analysis.

The countries impacted by a change should come from more than one geographical region to ensure a range of countries were involved. A country was in scope if it had 10 or more changes approved during 2018–2020, which was the minimum number for which a percentage analysis is considered valid.

Data were collected for over 5,900 postapproval CMC changes that translated to 20,000 country submissions with approvals in 2016–2020. Of these, over 790 changes in over 3,575 country submissions covering 97 countries were in scope. Changes were considered out of scope if they did not use the highest assessment impact regulatory process (e.g., Type IA/IB/CBE30 or notification in a country with a prior approval category) or if the change was only applicable in a single region.

Because the duration to submit, review, and approve in each country was variable, depending on the type as well as on the BoH prioritization of change, two representative durations were determined: the duration after the first global approval for a postapproval CMC change to achieve a 50% probability of approval and the duration after the first global approval for a postapproval CMC change to achieve a 90% probability of approval. For each country, the durations measured showed a skewed distribution,

Figure 2: Consolidated view of all in-scope country durations (as described in Table 1) and color coded by region.



meaning that averages and standard deviations were not applicable. Figure 1 shows a hypothetical example of a skewed distribution and the indicative position of the duration giving a 50% chance of approval and a 90% chance of approval.

The duration required to achieve a 90% probability of approval of a postapproval CMC change in a country (after the first global approval for that change) reflects the increased complexity required to manage the supply chain for these products and the concomitant impact to supply chain reliability. The duration to achieve a 90% probability of approval of a change was chosen because capacity and inventory management can effectively meet extended durations for the remaining 10% of approvals through stock builds. The duration to achieve a 90% probability of approval is simple to calculate and can be comparable across global companies and through time.

RESULTS

Figure 2 shows all the durations from first approval for a change to each country approval for that change (as described in Table 1) from the 3,575 in-scope country submissions. The skewed distribution is clear. The tail of approvals taking longer than 36 months can be seen. The long tail is the source of the greatest complexity for manufacturing operations.

For 47 of the 97 countries (48%), the time needed to achieve a 90% probability of approval of a change was ≥ 24 months but < 36 months after the first BoH approval for that change. There was a 50% probability of approval of a change in 94 of 97 countries within 24 months and all within 36 months of the first BoH approval for that change.

Table 2: Countries where the duration was ≥ 36 months after the first BoH approval for that same change.

Country	Region	Duration from First BoH Approval to Country Approval (months)	Data Points
Botswana	AFME	51	14
Jamaica	LA	48	29
South Africa	AFME	45	24
Kuwait	AFME	43	49
Oman	AFME	41	26
Jordan	AFME	40	31
United Arab Emirates	AFME	40	45
Iraq	AFME	39	39
Morocco	AFME	38	41
Dominican Republic	LA	37	72
Curacao	LA	37	43
Namibia	AFME	36	26
Panama	LA	36	61
Kosovo	EMEA	36	63
Palestine	EMEA	36	41

Figure 3: The cumulative percent of countries within each region against the duration needed to cover 90% of changes (as described in Table 1).

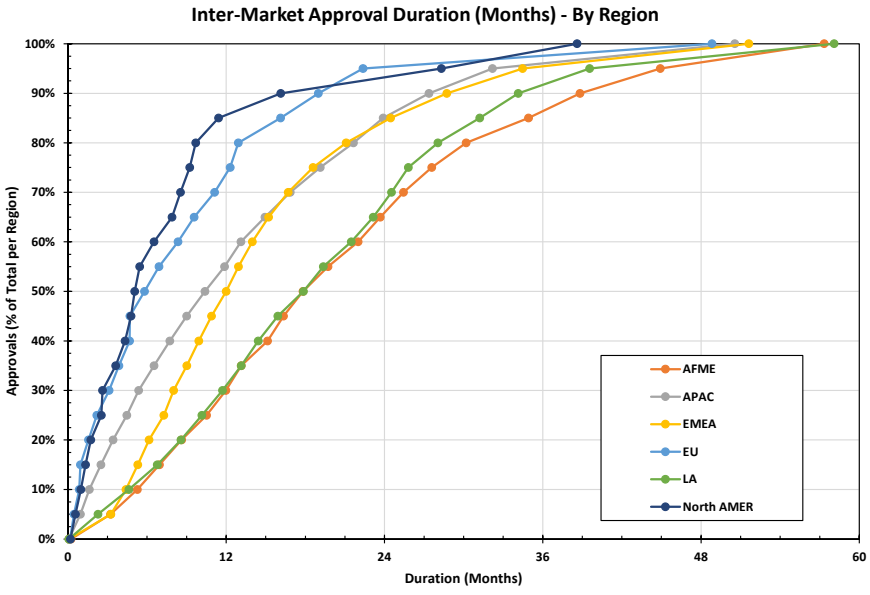


Table 2 shows the time needed to achieve a 90% probability of approval of a change (after the first approval for that change) for each of the 15 countries (15%) where the duration was ≥ 36 months after the first BoH approval for that same change. The durations were measured from first BoH approval for a change to that individual country's BoH approval for that change.

Figure 3 shows the cumulative percent of approvals by region against the number of months needed to achieve BoH approval after the first BoH approval for a change. It shows the spread of durations by region. For example, in North America, it takes approximately 16 months to achieve approval of 90% of submissions (after the first approval for that change), whereas in AFME it takes approximately 39 months to achieve the same milestone.

DISCUSSION

It is well known that it can take several years to achieve BoH approval for a single postapproval CMC change [2, 3]. The results of this current assessment measure the duration for BoH approval on a per-country basis for approvals received over a three-year period. Included in the duration to approval for each country affected by the same change are the relative impact of the change requirements in addition to the first country, constraints on submission times, and the impact of queries on approval time and the BoH assessment duration.

The time from first country BoH approval for a postapproval CMC change through to achieving approvals in the other countries impacted by the same change is the time through which manufacturing and supply chain teams need to manage different product inventories. The longest durations are those associated with changes going through the most rigorous assessment category available within the country. Consequently, the focus of the analysis was on this subset.

The results show that there is a 50% chance of approval of a change in all but three of the 97 countries in less than 24 months after the first approval. These 50% generally do not represent the main source of supply management challenges. Hence, it was necessary to establish a measure that captured the changes that take longer to approve and are more likely to become supply chain management and reliability concerns. The duration to achieve a 90% probability of

Table 3: Examples of issues contributing to long durations and proposals to mitigate.

Factors Contributing to Long Durations	Proposals to Mitigate Prolonged Approval Times
The stability data required at submission can vary from zero to six months in US and EU to > 12 months in some countries.	Align requirements with global regulatory standards, e.g., ICH or a reference country.
Changes cannot be submitted during an ongoing agency review of a change or a renewal (e.g., Brazil, South Africa), requiring sequencing and prioritization of submissions.	Create capacity by adopting GRP. Match requirements to the implications for patients, enabling parallel submissions.
The requirement for BoH approval regardless of the level of risk associated with a submission (i.e., no option for notifications). For example, a change covered by a notification in US or EU requires a new application in some countries.	Adopt a tiered approach such as that used in the EU or US.
Duration of BoH assessment of changes.	Reduce assessment durations by increasing capacity and adopting GRP, which includes mutual reliance and recognition, aimed at reducing workload for regulators and the time to approval.
Multiple iterations of BoH queries, many of which are not scientifically focused.	Improve risk-based approaches to regulatory reviews of postapproval changes, i.e., impact of change on product-critical quality attributes associated with quality, safety, and efficacy. In addition, consideration of mutual reliance and recognition, particularly when the change has already been effectively implemented in many countries globally.
BoH statutory framework, i.e., some BoH require a separate and specific licence for each manufacturing site. Consequently, any change in the manufacturing site requires a new submission rather than a postapproval change.	Legislation should be framed around the product rather than the site of manufacture.

approval of a change was chosen as the measure identifying supply chain management and reliability concerns.

In the dynamic global environment, the approval times for postapproval changes can be expected to change over time and may well differ between pharmaceutical companies based on different practices and approaches. Consequently, comparing results across companies and through time will establish an increasingly robust perspective of trends in global approval durations.

The results show that it can take over three years from approval in the first country to achieve a 90% probability of a country approval of that postapproval CMC change. Frequently during a three-year window, multiple CMC changes for a specific product will be submitted for global approval. Ostensibly, this significantly increases the complexity of managing multiple inventories and parallel supply chains for the same product simultaneously. This level of complexity increases the probability of affecting the reliability of supplies for every market.

Table 3 summarizes the factors that contribute to prolonged approval times based on experiences reported by Pfizer regulatory teams local to the impacted countries and proposes actions BoHs can implement to mitigate those prolonged approval times. The proposals are consistent with WHO GRP.

Existing regulatory frameworks

In the 1950s and 1960s, the WHO published documents outlining how countries should set up a regulatory framework to control pharmaceuticals and ensure the safety of their subjects. In parallel, the certificate of a pharmaceutical product (CPP) process was developed, enabling certain regulatory authorities to confirm approval and thus serve as reference for the basis of approval for products scheduled for import into other countries. Because regulatory legislation in different countries has developed independently, many different and sovereign approaches have evolved [7].

Reducing the prolonged duration for global approval of postapproval CMC changes will require improved alignment of data requirements; adoption of appropriate risk-based assessments that are proportional to the risk of a change to the critical quality attributes associated with product quality, safety, and efficacy; and alternatives to address BoH capacity constraints, i.e., mutual reliance and recognition, including cooperation between countries in evaluation.

These needs are all consistent with WHO GRP for regulatory oversight of medical products and "good reliance practices in regulatory decision-making for medical products" as well as the work of ICH covered in the mission statement and such publications as ICH Q12 "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" [1, 4, 8]. ICH Q12 provides a framework demonstrating how increased product and process knowledge can contribute to a more precise and accurate understanding of which postapproval changes require regulatory submission (Established Conditions). Postapproval change management protocols can be used to gain agreement among regulators about which requirements can be used to demonstrate acceptability of a change. In both cases, the level of reporting categories for changes can be agreed upon in advance.

Categories of change

The US and EU (among others) have developed categories of change depending on the change type and associated risk, with a clear set of requirements and timelines [9]. Some of these

categories can be handled through notifications or annual reports rather than through prior approval applications. The EU has adopted procedures where the evaluation by one or more countries is recognized by other countries in the group (i.e., the Centralized, Mutual Recognition (MRP), and Decentralized (DCP) procedures).

In recent years, several countries have adopted the EU approach in terms of categories and filing types (e.g., South Africa, some Gulf countries) and introduced forms of cooperation and reliance to reduce the assessment burden across the group (e.g., the Gulf Cooperation Council, Association of Southeast Asian Nations). Unfortunately, some countries also retained their local requirements, and most did not implement the associated review timelines. Few ROW countries have published commitments to assessment durations. In some instances, the capacity of the regulator to process the changes submitted appears to be incompatible with reasonable assessment durations. Adoption of GRP would help balance resource and capacity in these countries.

Some countries have attempted to mitigate the long duration to BoH approval by introducing a process by which a special import permit can be requested when the time to BoH approval is impacting continuity of supply. However, organizing these permits demands additional time and capacity that should not be needed if the regulatory framework and associated infrastructure in those countries was consistent with GRP.

Approaches should be adopted that are consistent with GRP and provide alignment, clarity, and consistency of requirements, submission types, and appropriate regulatory timelines in accordance with risk-based assessments of postapproval CMC changes. Global adoption of GRP encourages manufacturing innovation by removing barriers to continuous improvement and ensures reliable and sustainable supply of medicines to patients globally.

CONCLUSION

This exercise provided a comparative assessment of global approval times for postapproval CMC changes between 2018 and 2020. The results highlight the manufacturing and supply complexity associated with prolonged global approval times for each postapproval CMC change. In addition, the duration to achieve a 90% probability of approval of a change in a country represents the cohort of changes likely to be associated with supply issues and increased manufacturing complexity.

The finding that 15% of the 97 countries evaluated can take ≥ 36 months from first approval for a particular postapproval CMC change through to having a 90% chance of approval for that change in all other target countries represents a challenge for industry and the patients it serves. That the data obtained indicates that 63% of countries need ≥ 24 months to have a 90% chance of approval should also be considered to support advocacy in this area.

Implementing global best practices in medicines regulation to reduce the time from first to last approval for a global postapproval CMC change would minimize the cost of managing CMC changes for both regulators and industry. Such implementation would also reduce waste, create a more robust supply chain, and increase the alignment of products dispensed to patients globally.

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AIR SPEED QUALIFICATION: At Working Position or Working Level?

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The new European Commission GMP Annex 1 "Manufacture of Sterile Medicinal Products" and the equivalent Annex 2 from the World Health Organization (WHO) triggered a discussion in ISPE's Germany/Austria/Switzerland D/A/CH Aseptic Processing Community of Practice (CoP) Steering Committee about where to qualify air speed: "at working position" versus "at working level." This article provides background knowledge from literature and data from experiments to enhance the discussion.

REGULATORY BACKGROUND AND CLEANROOM AIR VELOCITY

In 2015, the authors of the Concept Paper on Revision of Annex 1 decided to harmonize the regulatory framework globally, including established methodologies such as those from the International Organization for Standardization (ISO) [1]. The European Commission (EC), the Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme (PIC/S), and the WHO agreed to develop one common updated "Annex 1" for the manufacturing of sterile medicines.

After a long drafting and harmonization phase, the EC published their new GMP Annex 1 [2] in August 2022. This was followed in September 2022 by the publication of the PIC/S's identical Annex 1 [3]. Lastly, the WHO published the new guideline under their framework in January 2023 as Annex 2 [4]. Unfortunately, in the WHO version, a couple of words are different from the EU and PIC/S Annex 1 versions, i.e., "working position" versus "working level" in chapter 4.30.

The setpoint for "proper" air velocity in cleanroom systems is documented in standards and regulations as 0.45 meters per second, plus or minus 20%, which is from 0.36 m/s up to 0.54 m/s. The initial determination tracks back to Willis Whitfield, a cleanroom pioneer at Sandia National Laboratories [5, 6]. From his research, the 0.45 m/s recommendation made its way into the US Food and Drug Administration (FDA)'s "Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice" [7] and into the EC GMP Annex 1 "Manufacture of Sterile Medicinal Products" in 2003 [8].

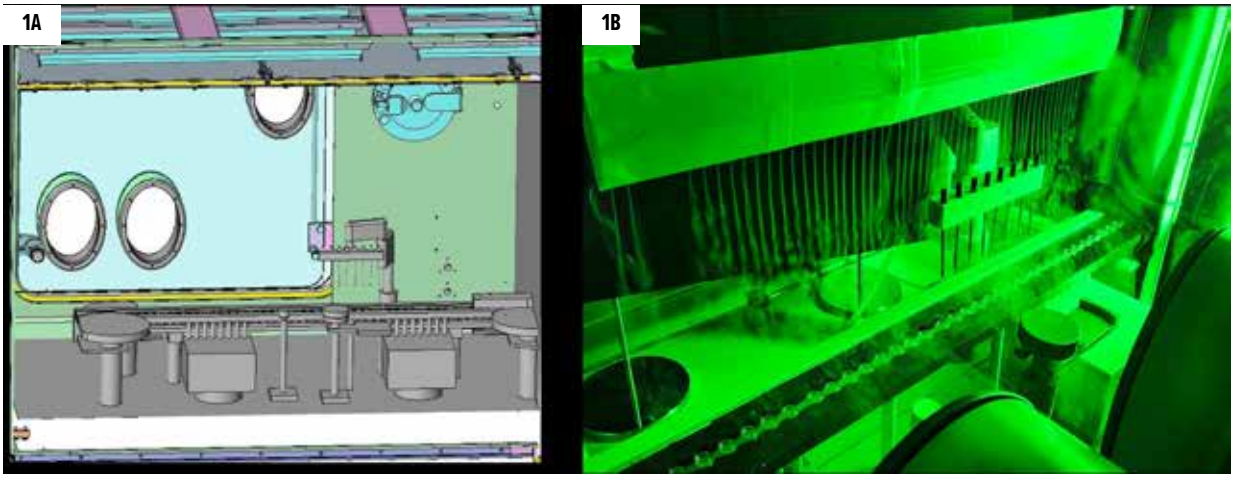
When an air velocity of 0.45 m/s for cleanroom settings became a guidance value in many standards and regulations, this started a discussion about where to measure it. In a 2009 *Pharmaceutical Engineering®* magazine article, Mason, McGarvey, and Spearman reported air speed measurements and air flow patterns in conventional cleanrooms with obstacles in the room, which caused obstruction of the unidirectional air flow [9]. The authors of the article used a thermal anemometer and analyzed air velocity changes in environments with these obstacles, then concluded that air velocity measurements should take place close to a high-efficiency particulate air (HEPA) filter face for better reliability and repeatability [9].

In 2015, the FDA published a guidance manual [10] that provided questions for inspections, including:

- Is the air flow in critical areas unidirectional when delivered to the point of use?
- At what velocity?
- Is velocity determined at the critical work height and at the filter face?

The preceding questions do not refer to a specific air velocity, but only to perform measurements at these two locations. But it is

Figure 1: 3D CAD drawing of 1A) isolator/vial filler model and 1B) physical setup for smoke study.



likely that interpretations in practice refer to footnote 5 from FDA Aseptic Guidance 2004 [7]: "A velocity of 0.45 meters/second has generally been established, with a range of plus or minus 20 percent around the setpoint."

EXPERIMENT SETUP

A wooden model of a vial filler/stoppering machine (Syntegon ALF 5080) in a real stainless steel straight double-wall isolator was used as the basis for the simulation as well as for the smoke studies and air velocity measurements. Some compromises had to be accepted because the vial filler model did not perfectly fit into the isolator. By cutting parts at the outfeed of the vial filler model and placing a wooden blind into the isolator to compensate for isolator-specific arrangements, a reasonable adaptation to the air flow properties of the "real vial filler in its own isolator" could be achieved. Figure 1 depicts a computer-aided design (CAD) drawing of the isolator with a vial filler model inside and a photograph of the physical setup for air flow visualization by smoke study.

The focus in all experiments was placed on the core filling section: particle counter, active microbial air sampler, fill needle bar with actuator, and transport system, including tare and gross weighing scales. The wooden model comes with some shape simplifications, but the main geometries were identical to the real machine parts, only less detailed. The wooden model used in this study represents a "worst case" scenario for air flow, because the wooden parts are a bit more robust in the contours and have no aerodynamic openings compared with real parts made from stainless steel.

The isolator was built in 2008. The internal volume is approximately 10 m^3. The heating, ventilation, and air conditioning (HVAC) system is capable of conditioning up to 3.850 m^3 of fresh air per hour. An air pattern deviation from typical installations could not be avoided: In the isolator applied for this study, a bold frame mount for the textile air diffuser with an outdated design was installed, which caused a slipstream drag reaching down to the open containers. This can be seen in almost all graphics, but it is located at the left side (infeed side) of the fill station and does not interfere with the air flow situation and the measurement in fill cell core.

The air speeds were set and controlled at the measurement point according to Annex B.2 of ISO Standard 14644-3: 150 mm below the textile air diffuser [11]. The investigations were focused on one of the most critical positions for the quality of the products in aseptic manufacturing: point of fill with open containers and openly exposed drug product.

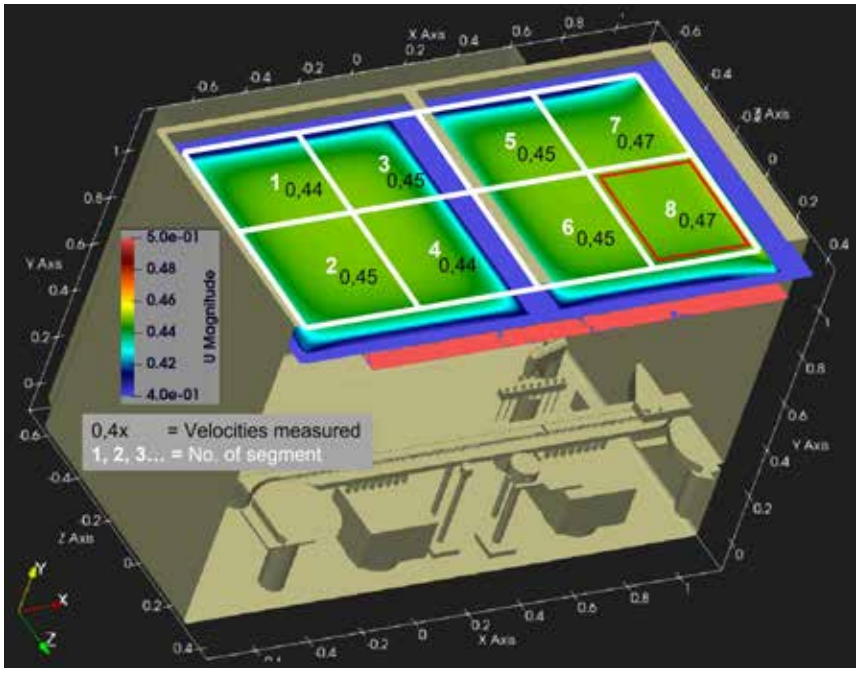
SIMULATION SETUP

The simulation was conducted using OpenFOAM 5.x, a free and open-source computational fluid dynamics (CFD) software package. The simpleFoam solver was used for solving the Reynolds-averaged Navier–Stokes (RANS) equations for a stationary, incompressible flow. The mesh was generated using the hexdominant method with the preprocessing tool SnappyHexMesh. This method involves creating a structured mesh with hexahedral cells that conform to the geometry of the object being simulated. The boundary cell size was set to 2.5 mm to ensure a sufficiently fine mesh near the walls and other areas of interest.

Solver

The simpleFoam solver is capable of simulating both laminar and turbulent flows. For turbulent flows, models such as the k-epsilon or k-omega shear stress transport (SST) models are used to account for the effects of turbulence on the flow. In this simulation, the k-omega SST turbulence model was used. This model considers the effects of both laminar and turbulent flows. And it can provide a more accurate prediction of the turbulent flow structure compared with the k-epsilon model. The model consists of two equations: one for the kinetic energy (k) and one for the specific

Figure 2: Air velocity distribution in XZ plane at 0.45 m/s and 150 mm from the air diffusor.



The setpoint for "proper" air velocity in cleanroom systems is documented in standards and regulations as 0.45 meters per second, plus or minus 20%.

dissipation rate (omega). These equations are augmented with the RANS equations to account for the effects of turbulence on the flow. The model also uses a wall function to model the turbulent layer near the wall.

SIMPLE Algorithm

The Semi-Implicit Method for Pressure Linked Equations (SIMPLE) algorithm is a widely used algorithm for solving the Navier–Stokes equations for incompressible flows.

The algorithm consists of the following steps:

1. Initialization: The pressure and velocity are initialized on a coarse mesh.
2. Pressure calculation: The pressure is calculated using the pressure Poisson equation.
3. Pressure correction: The corrected pressure is updated using the continuity equation.
4. Velocity correction: The velocity is updated using the corrected pressure and the Navier–Stokes equations.
5. Convergence check: The error is calculated and compared to a specified tolerance level. If the tolerance level is reached, the algorithm stops. Otherwise, the algorithm proceeds to step 2. Visualization of flow velocity, turbulent kinetic energy, and streamlines use Paraview 5.11.0.

Two velocity components, U_{mag} and $U_{y,}$ are visualized using the slice function to cut through the domain and show the velocity distribution on a 2D plane. In the simulation, 13 different air speeds were computed (0.1 m/s to 1.0 m/s in steps of 0.1 m/s; plus 0.36 m/s, 0.45 m/s, and 0.54 m/s), from which five were shown in this article: 0.20 m/s, 0.36 m/s, 0.45 m/s, 0.54 m/s and 0.90 m/s.

The turbulent volume-specific energy k (as a representative for turbulence) is visualized by isometric projection with $k = ½ \times (u')^2 = 0.0004$ J/m³. This value was chosen to display turbulence effects over the complete range of air velocities: from 0.2 m/s up to 0.9 m/s. The variable u' represents the average scalar velocity.

Air Velocity Measurement

All air velocity measurements were performed with a calibrated impeller anemometer (model Testo 480) equipped with a 100-mm-diameter wheel. This wheel was placed in a horizontal

position to measure the Y vector only. The sterile air diffuser in the test isolator was segmented into eight areas. To show the air distribution for each adjusted air velocity in XZ area (horizontally), the wheel was positioned in the center of these eight areas, 150 mm below the sterile air diffuser (see Figure 2).

For vertical air velocity mapping, the anemometer was placed in the center of area 8, which was located to the right (outfeed) of the fill core at four different levels: 150 mm from entry plane, 300 mm from entry plane (both in the ISO range), 20 mm above 10R vial opening (which is 900 mm from entry plane), and 200 mm above vial opening (which is at the height of the fill needle bar in "at rest" position—or 770 mm from entry plane). Vertical air velocity measurement could not be performed at area 6 (fill needle bar area) due to interfering contours or at area 5 (area with static hot-wire anemometer) due to accessibility.

For air velocity measurements and the smoke study, the set of variations was limited on the high-speed side due to the fan power maximum (0.91 m/s at area 8) and was limited on the low-speed sector due to the lower sensitivity limits of the impeller anemometer. It was decided to take 0.2 m/s as the lowest air velocity, where the anemometer still worked precisely. As a result, a set of five speeds was applied: 0.2 m/s, 0.36 m/s, 0.45 m/s, 0.54 m/s, and 0.91 m/s.

Air Flow Visualization Studies

For air flow visualization, a smoke generator (type Antari MB-1) with Safex fogging fluid Extra Clean F&D (art. no. 20302005) was used together with a 20-liter aerosol buffer and a distribution lance of Syntegon-owned wing design. The smoke was transported by compressed air to the nozzles of the lance. The air pressure was adjusted to the air speed inside the isolator by maximizing the length of the smoke filaments.

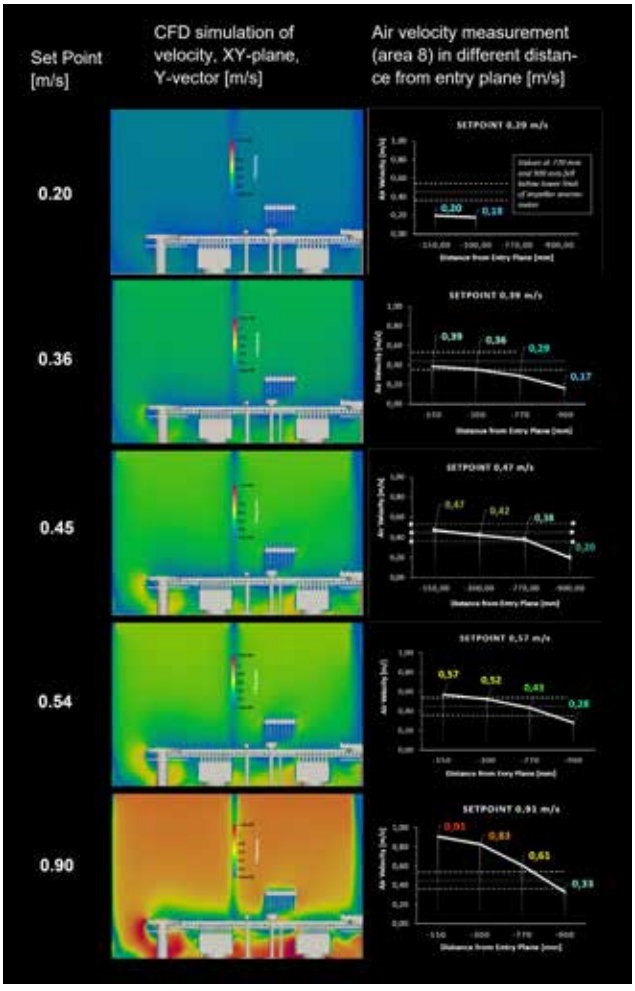
The pictures were taken with long shutter times (1/10 to 1/25 of a second) to catch the flow of smoke and direction. Limits at high air speeds came from low smoke density—higher air flow volumes in the isolator correspond to higher dilution factors. The aerosol concentration in the "smoke filaments" could not be increased further because condensation occurred and blocked the filament nozzles.

The illumination was provided from the opposite side of the camera position by a green LED light tube. For optimizing the photographic situation (i.e., maximizing the contrast of smoke against background), dark panels were used, which were optimized to not have a significant effect on the air flow (i.e., by shielding air flow from return air duct openings).

RESULTS

In the simulation, the air speed distribution at height level according to Annex B.2 of ISO 14644-3 [11] was computed 150 mm below the textile air diffuser. The result of homogeneity for 0.45 m/s (setpoint) is shown in Figure 2—the scale ranges from 0.40 to 0.50 m/s to show even minor differences. The air velocity variations are very small: 0.44 to 0.47 m/s across the isolator area.

Figure 3: Air velocity simulations (Y vector only) and measured air velocities in real machine/isolator model.

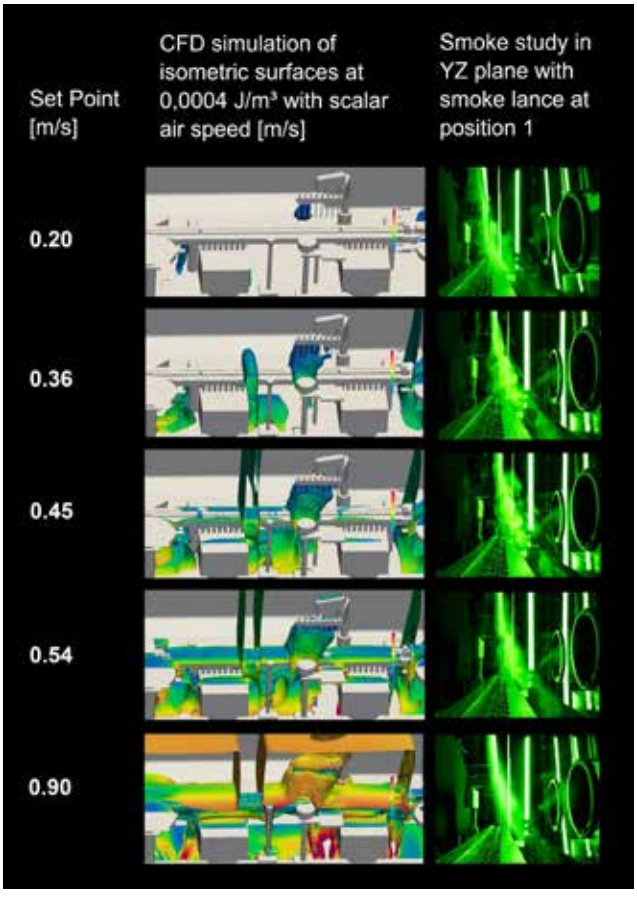


In Figure 2, an overlay with a grid of eight fields is also shown, whose centers were used for air velocity measurement with impeller anemometer. The measurement results are also written in values in the graphics. A good match between simulation and measurement can be seen. Both experiments indicate slightly higher air speeds to the right side (outfeed) of the isolator.

In Figure 3, a set of velocity simulation pictures and the results of the air velocity measurement in the real isolator are presented. The scale for air velocity is ranging from 0 m/s (dark blue) to 1.25 m/s (dark red).

The simulation graphs show the front view of the model (XY plane) and display the air velocities in Y direction only (Y vector). This represents the idea of unidirectional air flow (UDAF) as it is embedded in Annex 1: the air should come from the top—low in turbulence—and swipe over the open container and carry airborne or surface-bound particles into the filters (via return air ducts), if present and removable via an air flow. The filters or

Figure 4: Air turbulence simulations (isometric representation of turbulent energy loss at k = 0.0004 J/m³) and air flow visualization in real machine/isolator model.



openings of the return air ducts should be placed below the product because gravity should play against particles, whose trajectories are directing back.

A gradient of air velocity from the top to the bottom can be recognized for all air speed setpoints equal to or higher than 0.2 m/s. Air flow hitting a surface must go around the interfering contour, which means that the air velocity vector in orthonormal direction is at zero at the surface. The other vectors perpendicular to the impact direction will show high speed to get around the object. This principle is well known, i.e., from automotive streamline design or wing design for aircrafts.

Depending on the shape of the interfering object and the velocity of the UDAF, macroscopic eddies might be created, which take the air and residual particles, from the surface and bring them back above the objects, which results in an increased likeliness of particles being deposited into an open product container. This should be avoided.

Figure 3 clearly shows that even at the highest air velocity setpoint (0.9 m/s), the air velocity at vial height (20 mm above 10R vial opening) does not reach 0.36 m/s. Whether representing the "working height" for air speed measurement in the draft version of the new Annex 1 (2020) [12] or the "working level" in Annex 2 from WHO (2023) [4], the lower limit for recommended air velocity (guidance value) is not met.

This means that the speed setpoint needs to be more than doubled to achieve 0.36 m/s at 20 mm above vial opening. Much more turbulence was generated after taking the setpoint of air velocity from 0.45 to 0.90 m/s. At the 0.45 m/s setpoint, the air velocity in Y direction right above the open vials has not been more than 0.2 m/s. At a setpoint of 0.36 m/s (150 mm from entry plane), the air velocity at the vial opening dropped below the lower limits of the impeller anemometer: at roundabout 0.17 m/s.

Figure 4 represents turbulence level at different air velocity setpoints by displaying the isometric projection of a turbulent energy loss at k = 0.0004 J/m³. The color code represents the air speeds (scalar values) at these isometric surfaces in a range from 0 to 1.25 m/s. As a comparison, pictures of the smoke study at those air velocity setpoints are depicted in the graph.

With rising air velocity, the totalized area of turbulent energy loss increased significantly and air speeds at these areas got higher. A critical situation might come with the turbulence getting more voluminous (i.e., below the fill needle holding bar) and migrating from below the transport system/below vial level to "at" transport system or even above.

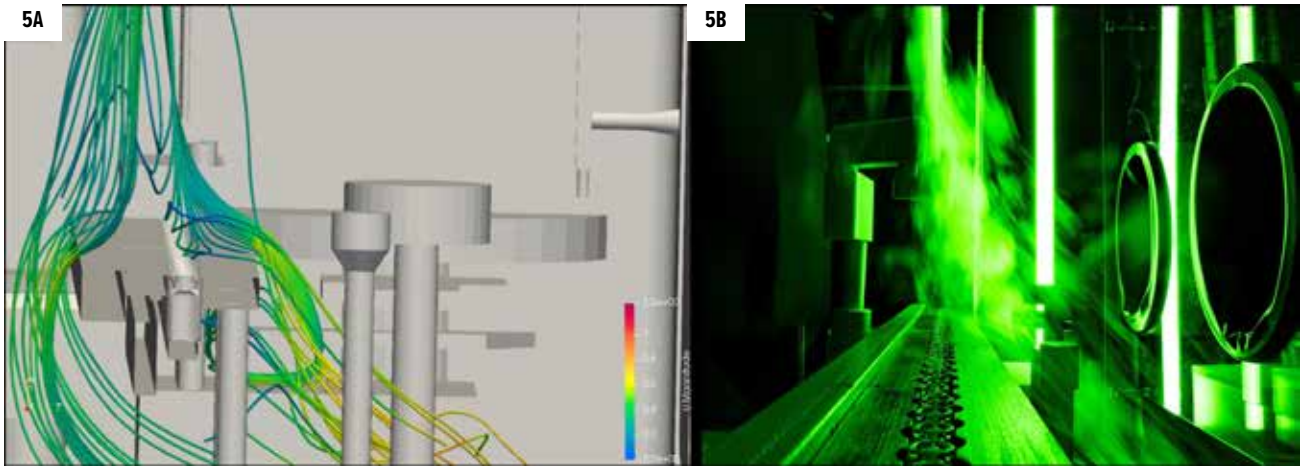
The series of smoke test photographs at different air velocity setpoints in Figure 4 reveal the air flow design inside of the isolator. The smoke lance was placed right above the fill needle bar: at 0.2 m/s setpoint, smoke filaments touched the transport system and swept over the open containers. While increasing airspeed, cross flow directly to the return air openings was generated, with little or no air touching the row of vials (at 0.90 m/s).

Figure 5A shows the situation at 0.45 m/s with streamlines coming from the smoke lance, which was relocated slightly behind the fill needle bar (compared to position in Figure 4 with location right above fill needle bar). Firstly, this illustration reveals the air flow hitting the vial transport and going around this barrier. Secondly, the air velocity close to the open containers was lower than 0.36 m/s (shown in the color code in the legend). Last, but not least, in Figure 5A, an eddy is visible on the outfeed star wheel (in the background on the right side of the transport). Considering that the wooden model represented a worst-case scenario, this situation in grade A areas should be avoided if possible. At 0.45 m/s, the simulation (5A) showed that the eddy stayed well below transport level.

CONCLUSION

The results show that the location of the air velocity sensor has a significant impact on air flow dynamics, especially in combination with the air flow value requirement of 0.45 m/s +/- 20% specified in Annex 1 (EC GMP [2] and PIC/S [3]) and Annex 2 (WHO [4]). The air velocity decreases from the top of the cleanroom (restricted access barrier systems [RABS] or isolator) to the bottom/machine plate (see Figure 3).

Figure 5: 5A) streamline illustration of air flow at 0.45 m/s and 5B) enlargement of smoke study picture from Figure 4 at same air velocity.



This study was performed with a straight wall isolator. Results may differ with inclined window barrier systems, because of smaller airflow column cross section of return air duct openings compared with cross section at air entry plane. But the major principles stay the same and the general conclusion applies also to this type of isolator or RABS design. If the "working level" discussed in Annex 2 (WHO [4]) means at height level of filling operation (represented in this publication by a level 20 mm above 10R vial opening), the air velocity setpoint must be higher than 1.0 m/s at the level set by ISO Standard 14644-3 [11] to achieve the required air velocity at point of fill. The higher air volumes would then need to be conditioned and recirculated, and the air flow design adjusted to minimize crossflow.

And finally, it would also create turbulence in the grade A zone. In the setup represented in this article, at higher velocity setpoints (i.e., 0.90 m/s), the turbulence occurred below the fill needle holder, on the transport system, and near isokinetic probes and viable samplers (see Figure 4). The unidirectionality of air flow at lower velocity setpoints was much better. At lower velocities, air flow can still carry particles away from open containers, without risking turbulence or even macroscopic eddies in the fill environment, as shown in Figure 5. This is also in accordance with the findings of Mason, McGarvey, and Spearman [9] and the results from earlier studies cited by Brande, Milholland, and Haycocks [6].

Paragraph 4.30 of the new Annex 1 (EC GMP [2] and PIC-S [3]) requires: "Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components *at the working position* (e.g., where high-risk operations occur and where product and/or components are exposed)." The wording "at the working position" can be interpreted as "at working level" and/or where working (processing) take place, i.e., at the filler station or at the stoppering station.

In the draft version of the Annex 1 from 2020 [12], it was proposed under paragraph 4.32: "Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components *at the working height* (e.g., where high-risk operations occur and where product and/or components are exposed)." By changing "working height" from the draft version of the new Annex 1 from 2020 to "working position" in the final document [2], the EMA working group on Annex 1 indicated that they clearly did not mean the height level as "working position," but rather the location on the machine where quality-critical processes are located.

> When an air velocity of 0.45 m/s for cleanroom settings became a guidance value in many standards and regulations, this started a discussion about where to measure it.

Measurement at ISO level ("150 mm to 300 mm from the entry plane") and compliance with regulatory air velocity corridor at this level has even more advantages: It guarantees reproducible measurement, because handling and machine movements do not interfere with the direct environment of the air velocity sensor that is creating measurement deviations. Sensors at this height level are less at risk to be damaged during manual glove interventions. And finally, the CO_2 footprint of the cleanroom enclosure operation is much lower because lower air volumes will be conditioned and recirculated at lower speeds.

The authors propose staying with the air velocity setpoint according to the new Annex 1, specifically, "at working position," which means where quality-critical processes take place, i.e., filling or stoppering. But air velocity (0.45 m/s +/- 20%) should be measured and controlled at the level specified by ISO Standard 14644-3, which is 150–300 mm from the entry plane. Air flow visualization studies must correlate with Annex 1 to effectively sweep away particles from the air above the open containers and by reducing turbulence in critical areas as much as possible.

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CONSIDERATIONS FOR A Decentralized Manufacturing Paradigm

By Marquerita Algorri, PhD, Ting Wang, PhD, Jocelyn X. McQueen, MS, and Nina S. Cauchon, PhD

The biopharmaceutical industry must develop and implement innovative ways of working to be effective and efficient in the current healthcare ecosystem, in which high-quality medicines, adaptability, and assurance of supply are of critical importance. There are regulatory strategies and technologies emerging to address these challenges, but further progress must be made to fully harness the advantages of advanced and decentralized manufacturing techniques.

In comparison to traditional large-scale manufacturing operations, decentralized modes of manufacturing can be more agile, more transportable, and tailored for specific modalities or production processes. However, although the supporting technologies needed to enable decentralized manufacturing have continued to advance over the past decade, the regulatory expectations for submission data packages must also evolve, using the technology transfer of a biologic as a relevant example, to make implementing decentralized manufacturing more practical and attainable for manufacturers.

This article presents relevant insights on the current regulatory and technical landscape for decentralized manufacturing, with select examples of current applications, and discusses perspectives on evolving and adapting the current regulations to meet future capabilities.

ADVANCED MANUFACTURING

In the biopharmaceutical industry, "advanced manufacturing" refers to the operating models and supporting technologies that aim to transform or modernize the production of therapeutic products [1–3]. Though traditional large-scale batch modes of operation can be used for many small and large molecule drugs, such that manufacturing strategies can be designed as fit for purpose, alternative strategies to traditional manufacturing methodologies are increasingly needed to operate more efficiently, keep pace with market demands, and enable the commercialization of advanced or personalized therapies. Specifically, in biopharmaceutical development, there is a continued trend of new modalities with increasing complexity and smaller batch sizes, which requires retooling traditional manufacturing approaches for those applications.

The COVID-19 pandemic highlighted the need for responsive and agile manufacturing systems that can reliably perform and meet supply chain demands in a rapidly changing environment. In response, modes of manufacturing that are decentralized, transportable, and increasingly configurable have emerged as areas of interest and investment for both industry and regulators. These new operating models can help enable and accelerate the efforts of Pharma 4.0™ toward the implementation of smart manufacturing, digitization, and automation [4, 5]. Additionally, reducing shipping limitations—such as packaging, storage, and transportation durations—helps speed up patient access in certain instances while ensuring there is no negative impact to the product's critical quality attributes (CQAs).

Although the novelty of these modes of manufacturing has led to some definitional ambiguities, initial working definitions and terminology have been drafted by several regulators, trade organizations, and subject matter experts. There are several operating models that can potentially be categorized under "decentralized" manufacturing, including distributed manufacturing (DM), modular manufacturing (MM), and point-of-care (POC) manufacturing. The following working definitions are useful in establishing foundational understanding; however, harmonization of terminology is ultimately needed to develop cohesive and supportive regulatory frameworks across regions.

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Herein, DM refers to a manufacturing model in which many units or facilities are disseminated across different geographical areas [6, 7]. DM facilities may produce similar or identical products under a unified pharmaceutical quality system (PQS) or operate as independent units with different outputs [6]. MM describes a platform in which unit operations and/or manufacturing activities are conducted in interchangeable components or modules [8, 9]. Modules can be switched in or out to meet the current needs of the facility, including single-use materials as appropriate, to complete different types of production.

Currently, most modular facilities operate in a single fixed location that leverages the production flexibility granted by the modules, but modular operations may also be transportable and capable of enabling DM in a portable-on-demand (POD) format [10]. Similarly, POC manufacturing describes production at or near the location of the patient. POC manufacturing solutions can consist of modular and distributed approaches in which modules or units are geographically dispersed across local patient hubs.

Fit for use is a critical factor that companies must evaluate when selecting a manufacturing operating model. In particular, DM and POC manufacturing models are considered a natural fit to produce many cell and gene therapies. As a result, there has been substantial prior discussion on DM and POC manufacturing that has focused on solving for logistical challenges in producing highly individualized therapeutics. However, DM, MM, and POC manufacturing may be suitable for other types of biologic products as well, including those that are currently produced in large-scale, centralized manufacturing facilities, such as monoclonal antibodies (mAbs).

For example, fill-finish operations for products using prefilled syringes can be performed close to the point of distribution or point of care to address transport challenges caused by stability issues that require ultra-low-temperature storage and shipping conditions. Similarly, having multiple sites of manufacture or distribution, or flexible modules that enable reconfiguration of a facility, can help ensure patient supply close to the point of use and can manage localized drug supply shortages across product types.

Here we focus on the potential uses for DM, MM, and POC for biologics, highlighting emerging technologies, proposed changes to the regulatory framework to enable implementation, and anticipated future developments in the technological and regulatory landscapes.

EMERGING TECHNOLOGIES AND RECENT APPLICATIONS

Agility, flexibility, and reproducibility of a biomanufacturing operating model are enabled and empowered by a variety of advanced technologies including, but not limited to, single-use technology (SUT), process analytical technology (PAT), continuous manufacturing (CM), POD, and Pharma 4.0™ technologies. These emerging technologies promote local and highly flexible production that is as robust as, or in some cases superior to, traditional testing and manufacturing in terms of consistency and control through a number of mechanisms. However, in addition to the advantages of the emerging technologies, there are also various challenges for industry and regulators when incorporating these newer concepts into the traditional regulatory submission framework during the product life cycle.

An overview of the concepts, advantages, technical challenges, and considerations associated with the implementation of the innovative technologies is provided next. Select applications of the aforementioned technologies in the context of decentralized manufacturing are provided in Table 1. Previous articles have discussed these applications and biopharmaceutical industry examples at greater length and detail [3]. However, herein, we summarize prominent enabling technologies; offer some recent examples of real-world applications in POC, MM,

Table 1: Selected examples of real-world applications

Manufacturing Type	Company/Institution	Product Information	Key Facts of Facility and Manufacture	Location	Phase
Point-of-care manufacturing (POC)	University of Maryland, Baltimore County [33]	Granulocyte colony-stimulating factor (G-CSF)	• Portable platform is called on-demand biologics manufacturing (bio-MOD) • Used for cell-free protein expression and subsequent purification • Size of a suitcase or laptop • GMP-like conditions • PATs deployed for real-time quality control • The entire process takes less than half a day vs. weeks to months for cell-based manufacturing processes	Can be installed in all local hospitals, fire stations, pharmacies, and other potential evacuation centers	Development
POC	Dmitry Rogachev Center and University Hospitals Seidman Cancer Center [34]	Anti-CD19 CAR (CAR19)-T cells	• Manufactured under cGMP at two clinical sites • Deployed closed, automated cell processing platform CliniMACS Prodigy with associated materials and reagents • Identical device, reagents, and materials were used between two clinical sites	Moscow, Russia, and Ohio, US	Phase 1

Manufacturing Type	Company/Institution	Product Information	Key Facts of Facility and Manufacture	Location	Phase
POC	CellPoint B.V. [35]	Cell therapy (GLPG5102)	• In a collaboration with Lonza using a novel POC supply model • The proprietary platform consists of: ▫ CellPoint's end-to-end xCellit workflow management ▫ Monitoring software ▫ Lonza's Cocoon platform, which is a functionally closed, automated manufacturing platform for cell therapies	Europe (multi-center study)	Phases 1 and 2
POC	Orgenesis [36, 37]	Cell therapy	• Shipping-container-sized cGMP manufacturing facilities (POCenters) consist of Orgenesis mobile production units or labs (OMPULs) • Prefabricated, prevalidated, and closed system • Automated process to remove as many manual steps as possible • Easy to duplicate and scale out • Cost-effective (target to be 1/5 of current cost)	Regional hub supply centers in the EU and US that will serve medical centers within a four-hour travel radius	Development
Modular manufacturing (MM)	ADMA Biologics, Wildlife Pharmaceuticals, Emergent BioSolutions, BPI Labs, Singota Solutions, WuXi Biologics, FUJIFILM Diosynth Biotechnologies, and Genentech [38]	Across dosage formats and sizes including biologics	• Deployed Cytiva SA25 filling workcell, which is a standardized, fully closed robotic system for aseptic filling of vials, syringes, and cartridges • One of the companies achieved an industry-first FDA-approved commercial production with viable environmental monitoring (EM) during process simulations but routine viable EM • Control strategy includes two key segments: isolated environment and presterilized primary containers in sealed packaging	US, South Africa, Canada, and China	Clinical/ Commercial
MM	Janssen Pharmaceuticals in collaboration with Legend Biotech [39]	Cell therapy (CAR-T cells)	• A hybrid "conventional–modular" approach using iCON pods that heavily used prefabrication and modular construction • Retrofit within an existing open shell space • Completed construction within nine months with zero recordable incidents • Designed utility systems with a focus on sustainability	New Jersey, US	Clinical
MM	Sanofi [40, 41]	Vaccines	• A new production building includes multiple modular production facilities built around a central hub • Facility is called Evolutive Vaccine Facility (EVF) • Fully digitized biomanufacturing unit • $554 million US investment in the construction over five years • Capacity to produce three to four vaccines simultaneously and quickly switch to mono-production as needed • Designed to reduce energy consumption and will also be close to carbon neutral	Neuville-sur-Saône, France	Intended commercial
MM	Amgen [42]	Biologics (multiple products)	• Incorporates multiple innovative technologies into a single facility, such as flexible modular design and SUTs • Compared to conventional manufacturing, this facility has achieved: ▫ 1/4 of the capital cost ▫ 1/2 of the construction time ▫ 1/2 of the operating expense ▫ Reduced solid waste and usage of chemicals ▫ 76% reduction in CO_2 emissions ▫ 78% energy reduction ▫ 58% water reduction ▫ 16% of the size	Singapore	Commercial

Table Continues

Manufacturing Type	Company/Institution	Product Information	Key Facts of Facility and Manufacture	Location	Phase
MM	Genentech [43]	Biologics (multiple products)	• Targeted to open in 2025 • Leverages modular equipment, advances in SUT, automation, and digital manufacturing • Compared to conventional manufacturing, new facility will achieve: ▫ Zero plastic waste to landfill ▫ 14% less carbon ▫ 25% energy reduction ▫ 28% water reduction	California, US	Intended commercial
MM	Eli Lily and Company [44, 45]	Synthetic drug substance	• The modular production facility is called Small Volume Continuous (SVC) • Targets pipeline products with an annual volume less than 1.5 metric tons • The continuous unit operations are provided on mobile skids that can be interconnected and configured in multiple ways • Continuous process skids include plug flow reactors, continuous stirred reactors, distillation, extraction, filtration, and crystallization • Operating system is designed for "plug and play," which can be configured in multiple sequences and recognized by the distributed control system	County Cork, Ireland	Development
MM	Pfizer [46]	Sterile injectables	• The facility will be a multistoried facility with an estimated investment of $465 million • Features state-of-the-art modular aseptic processing (MAP) technology, equipment, and systems • The facility will be equipped with multiple sterile, self-contained mobile manufacturing lines	Michigan, US	Intended commercial
MM with distributed manufacturing (DM)	BioNTech [47, 48]	Vaccines such as Comirnaty	• Facility is called BioNTainer • A total footprint of about 800 m^2 • Modular factories housed in shipping containers • Consists of one drug substance and one formulation module • Each module is built from six standard shipping containers • Each BioNTainer has the capacity to produce 50 million doses a year • Can make a COVID-19 vaccine from start to finish, with fill-finish step left to local partners	Rwanda, Senegal, South Africa, and Australia	Intended clinical/ commercial

and DM complementary to technology transfers; and provide advantages and challenges to implementation in the current manufacturing, technological, and regulatory environments.

ENABLING TECHNOLOGIES FOR MM AND POC MANUFACTURING

Continuous Manufacturing

Description

CM is a single integrated process in which the input materials are continuously added and transformed during the process, with continuous output. CM can be applied to an individual unit operation; however, it most often refers to an integrated process consisting of two or more unit operations. CM is applicable to drug substances and drug products for synthetic entities and biologics [11–17].

Advantages and Considerations

CM improves manufacturing efficiency and flexibility. It reduces the manufacturing footprint, provides "right-size" production scales by adjusting process run times to meet demand, expedites technology transfers due to similarities in equipment and scale across sites, and is amenable to PAT, which support process validation and continued process verification (CPV). However, it may present increased system and validation complexity, e.g., PAT validation, and any upfront investment in equipment and expertise needs a business justification. Further, because CM is newly emerging, there is a need for more highly trained staff. It also may not be available at all contract manufacturing organizations (CMOs), especially for biologic drug substances; thus, outsourcing may not be an option.

Advanced Aseptic Technologies

Description

An advanced aseptic technology is an aseptic process or system in which design and automation are used so that direct human intervention from operators is not required or permitted during processing. Examples include a closed aseptic filling system, isolator, and robotic arm for aseptic filling [18–26].

Advantages

In advanced aseptic technologies, the equipment provides a robust sterile manufacturing environment and transportable solutions for DM aseptic manufacturing operations. These technologies also offer a combination of closed, connected process and the centralized control facilitates improved efficiency, safety, and compliance.

Challenges and additional considerations

In these technologies, minimizing microbial contamination relies on a foundation of system design and controls and requires careful planning, environmental monitoring, specialized facilities and equipment, and trained personnel. Integration, such as incorporating an isolator into a lyophilizer, can be complex and cycle time can be extensive. Closed restricted-access barrier systems (RABSs) and isolators are expensive compared to standalone systems. Additional stability studies may also be needed to ensure there is no impact to product quality from decontamination or cleaning products like hydrogen peroxide.

Portable-on-Demand Format

Description

POD refers to a type of "autonomous and portable" manufacturing facility with one or multiple units that house a defined set of pharmaceutical operations and that is variable in size. Examples include platforms as small as autonomous units placed within a facility and mobile production trailers for compounding to platforms as large as a prefabricated, self-contained GMP facility [3, 27].

Advantages

POD increases manufacturing flexibility, speed, and consistency. Duplication enables rapid scale-up and scale-out, new facilities can be constructed in less than 12 months, and isolated operation avoids cross-contamination. POD is suitable for a wide range of products, including oral solid dosage forms, mAbs, and cell therapy. The fit-for-purpose and reduced-size POD units promote green manufacturing. It can add functionality by establishing a new facility or repurposing or reconfiguring an existing facility.

Challenges and additional considerations

Challenges exist in understanding and mitigating mobility-related quality risk factors and adjusting PQSs to include additional engineering control considerations. POD creates new challenges in meeting existing regulatory standards such as the registration of a physical address. Due to the limitation of instrumentation and size when analyzing a sample on-site, analytical technologies supporting POD require further development and are continuously evolving. Regulatory divergence and local expectations may also serve to limit the extent to which the benefits of "lift and shift" or "duplicate and move" can be realized.

Single-Use Technology, System, Assembly, or Equipment

Description

SUT or SUSs are most commonly constructed with polymeric components, creating a system or unit operation that is designed for one-time or a single-campaign use and is subsequently discarded. Examples include bioprocessing bags (replacing glass flasks and tanks), single-use bioreactors and accessories (replacing stainless steel bioreactors), aseptic connectors, and transferring assemblies and filters [12, 28–31].

Advantages

SUT creates closed systems, which separates operators and rooms, enables aseptic transfer between containers, and mitigates the risk of cross-contamination. It also reduces environmental impact because it requires fewer chemicals and less high-purity water and heat. SUT has transformed bioprocessing in terms of design, scale, operation, control, and speed of incorporating innovations. It shortens the time required to build a manufacturing facility and develop a manufacturing process. In addition, SUT reinforces the GMP emphasis on equipment qualification, reduces facility footprint, downtime, changes over time, and increases manufacturing capacity.

Challenges and additional considerations

With SUT, control strategies and supply assurance are heavily dependent on supplier collaboration, for example in the areas of quality systems, component and container qualification, change management, and supply chain management. Risk assessments require additional considerations such as chemical compatibility between process solution and materials of construction, risk of extractables and leachables, and establishing material interchangeability and second sourcing to enable uninterrupted supply.

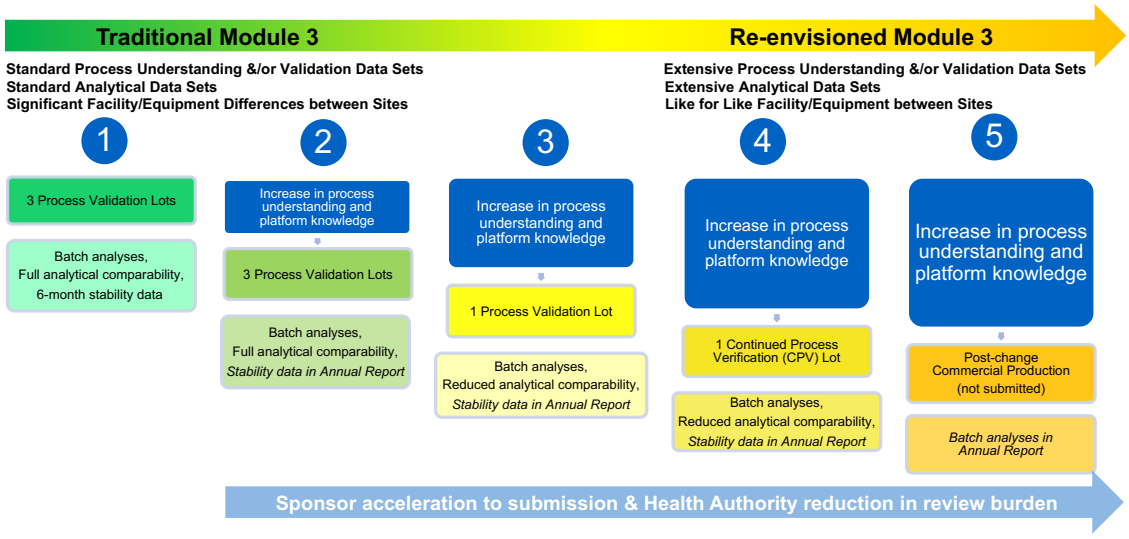
A functional equivalency to traditional approaches may be challenging to establish with SUT because of its limitations in oxygen and heat transfer, or limited usability in high-temperature and high-pressure processes due to materials of construction or limitation in available sizes to accommodate the same processing volumes as traditional equipment. Single-use assemblies may pose risks or cause defects due to material manufacturing, assembling processes, or transportation. Further, traditional manufacturing may need to be in place to mitigate the impact of unavailability of SUSs due to quality or supply issues, and strategies are required for the treatment, handling, and disposal of post-use waste.

Industry 4.0 Technologies

Description

Industry 4.0 technologies deployed in the biopharmaceutical industry center on the concept of capturing and connecting all

Figure 1: Re-envisioning Module 3 data packages for biologic technology transfers.



relevant data, and applying advanced analytics to the connected data to produce process insights so that ultimately the manufacturing plant can be automated with less human interaction. These technologies can include Internet of Things, artificial intelligence, robotics, and advanced computing [5, 13, 27, 32].

Advantages

Industry 4.0 technologies enhance manufacturing efficiency, manufacturing flexibility, and product quality. PAT enables real-time monitoring, which reduces or eliminates conventional in-process testing, enables real-time release testing (RTRT), and reduces production cycle times. Large-scale data analytics support process validation and CPV. Digital twins can be applied to better understand, evaluate, predict, and optimize process performance.

With these technologies, there's an abundance of data collected throughout the product life cycle, across sites, and across products, all with the potential to reduce certain repeated work in technology transfer. Feedback controls can be enabled through a combination of automation and predictive modeling. Compliance with quality and safety standards can be improved through the use of automation and robotics.

Challenges and additional considerations

However, Industry 4.0 technologies face a few challenges. Implementation can be challenging due to legacy systems integration, the disparate nature of hardware and software offered by a range of different vendors, enabling and/or establishing robust system foundation, and cultural change. They also potentially require a large initial capital investment and additional education and training to develop or upskill talent. Finally, analytical solutions, hardware, and software are still evolving to meet unprecedented levels of requirements in terms of functionality, robustness, validation, safety, and security.

RE-ENVISIONING TECHNOLOGY TRANSFER OF A BIOLOGIC TO NEW MANUFACTURING SITES

Within the biopharmaceutical industry, a philosophy held close by regulators and sponsors alike is that "quality should be built into the product, and testing alone cannot be relied on to ensure product quality" [49]. However, regardless of the quality built into a product by enhanced understanding of product CQA and critical processes and the material parameters that impact those CQAs, a significant amount of data generated by manufacturing and testing must be submitted by sponsors to gain health authority approvals.

The Past and Present

Historically, sponsors face the challenge of determining the amount of prior knowledge to be included in regulatory submissions [52], whereas regulators are hesitant to acknowledge or place value upon submitted prior knowledge. Thus, sponsors may end up repeating studies that could be viewed as confirmatory, or even redundant, to enable chemistry, manufacturing, and controls (CMC) changes. This can result in the generation of new data for a specific monoclonal antibody (mAb), for example, when the sponsor already has existing data on similar platform products and processes that supports the fact that the CMC change will result in a product of comparable quality.

We will use technology transfer from an approved sending site to a proposed receiving site as an example. First, facility fit and gap assessments of the process between the sending site and receiving site must be conducted. Then substantial time and resources are needed to run the same manufacturing process at the receiving site and test the resulting product in quality control (QC) laboratories or use emerging technologies, such as PAT or RTRT, to generate release and characterization data demonstrating analytical comparability.

Subsequently, the new data is authored into Module 3 (Quality) of the Common Technical Document and submitted separately to multiple health authorities worldwide for approval. The sponsor then waits to distribute product with the change(s) implemented over an approval window of four months—as in the case of the US Food and Drug Administration (FDA)—to six years or more—as in the case of health authorities that require major market approvals prior to submission, and/or the submission of data from more post-change lots and stability data over longer durations of time.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q12, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (2019), aims to simplify and harmonize life cycle management by identifying the types of changes that necessitate regulatory submission and by establishing risk-based reporting categories [53]. However, endorsement, adoption, and implementation of ICH Q12 has been challenging for regulators and sponsors when it has been restricted by local legislation or differing health authority feedback on a single science-based and risk-based data set. Consequently, sponsors continue to face hurdles, such as variable regulatory review timelines and heterogeneous supporting data packages for postapproval change management [54].

Although a complete package of fresh data is currently required for each mAb introduced to a new manufacturing site, it is unclear if this is a necessary or sustainable process for obtaining individual health authority approval for every technology transfer. Furthermore, this process becomes increasingly arduous in the context of DM, in which multiple manufacturing sites are generating data for the same or similar mAbs. Put simply, in situations where a sponsor has extensive manufacturing history, robust platform data, and a strong understanding of CQAs, the current regulatory framework affords no relief in Module 3 preparation by sponsors or review by health authorities. It takes the same amount of time for such a sponsor to get product to patients as it would for a sponsor who does not possess such process or product understanding.

This does not have to be the case because the foundation for science- and risk-based approaches exists. The ISPE *Good Practice Guide: Technology Transfer* (*Third Edition*) advocates for balance between risk management, resource management, and regulatory expectations [55]. It also aligns with science- and risk-based quality by design (QbD) principles described by ICH and recognizes that knowledge management and a robust quality culture are critical to successful technology transfer [55].

The Parenteral Drug Association (PDA) Technical Report No. 65: Technology Transfer (revised 2022), aims to standardize the approach to technology transfers, which would include conducting risk assessments, process comparisons, and knowledge transfers [56]. ICH Q9(R1), Quality Risk Management, describes how quality risk management should be used in the impact evaluation of proposed CMC changes, and in determining the appropriate actions needed prior to implementation of changes, including testing, (re)qualification, (re)validation, or communication with regulators [56, 57].

Practical utilization of these concepts to a larger extent within a more flexible regulatory framework could result in re-envisioned or nontraditional approaches to Module 3 preparation and review, enabling more efficient postapproval change management. This is particularly applicable in the setting of DM or POC manufacturing, for which the current regulatory framework places prohibitive hurdles to implementation. A science- and risk-based approach can and should be taken toward the data sets that need to be generated and submitted to health authorities to prove that quality is built into the product; specifically, that the biologic product manufactured from the new receiving site is analytically comparable to the product manufactured from the approved sending site.

Legal hurdles also exist, for example, in countries where health authorities prohibit dual sourcing, meaning the sourcing of a commercial product from more than one manufacturing site. Although it is acknowledged that the laws and regulations in many jurisdictions were not written for the potential of DM or POC manufacturing, such legal and regulatory hurdles are prohibitive of sponsors creating a DM or POC network, where similar or "sister" sites are used in different locations.

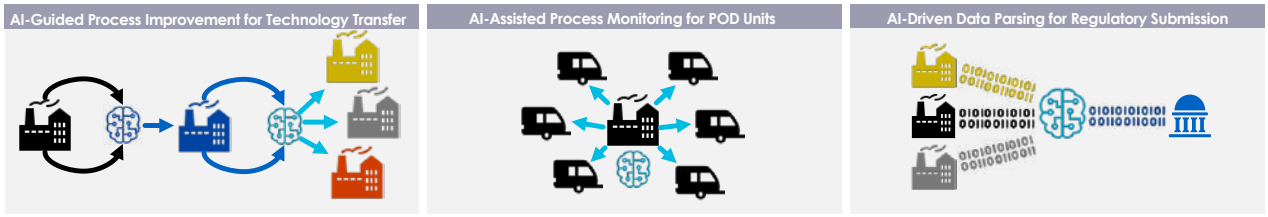
The Realized Potential

The COVID-19 pandemic highlighted the capability of sponsors and regulators to take science- and risk-based, nontraditional, approaches, which resulted in new perspectives. Both sponsors and regulators employed these approaches, which, in combination with close communication, expedited authoring and review durations, resulting in the accelerated use of COVID-19 vaccines manufactured by, for example, Pfizer and Moderna [58].

As an additional example, to increase manufacturing network capacity for the manufacture of a third-party COVID-19 therapy, Amgen engaged the US FDA regarding a science- and risk-based strategy for a mAb drug substance technology transfer [59]. Drug substance process validation data were generated in parallel to FDA review of meeting materials and a subsequent comparability protocol (or postapproval change management protocol [PACMP]). A final submission was negotiated to the downgraded reporting category of a change being effective in 30 days (CBE 30) supplement to submit the process validation data with reduced analytical comparability data.

A preapproval inspection (PAI) of the receiving site was not conducted by the FDA, likely due to the robust and credible historical clinical manufacturing experience of the mAb at, and the prior inspection history of, the receiving site [60]. This strategy enabled the ability to distribute product to the US market with the change implemented eight months earlier than with traditional Module 3 content and reporting categories. Applying this type of flexible approach to postapproval change management for DM or MM, as well as for other appropriate site transfers, would ensure that the lessons learned from the pandemic are utilized effectively.

Figure 2: Potential future applications of AI technology.



The Future

By applying the science- and risk-based strategies aforementioned, it is clear that more efficiencies can be gained, including lessening the review burden on health authorities. Although such strategies would directly enable sponsors to submit postapproval variations sooner, they would not immediately reduce Module 3 content. The success of science- and risk-based process, analytical, and regulatory strategies is contingent upon many important factors (the "how").

To demonstrate to regulators that a process is understood and in control, CQAs of the product will not be negatively impacted, and the safety and efficacy of the product will be maintained in patients, the sponsor must provide to the regulators detailed process and analytical comparisons (pre change compared to post change), clearly define the systems (i.e., the process, critical process parameters, raw materials, components, equipment, environment, testing methodologies, and/or technologies) from which the data sets are generated, and provide historical data (in the form of clinical, process development, process characterization data, and/or platform data) that support the change.

The concept of MM is a straightforward illustration—whatever is "modular" about the manufacturing, whether it be an entire room or a defined system within the manufacturing line, the module or system can be defined in narrative, images, and data. Then, this module or system, with defined inputs and environmental conditions under the PQS, can be used anywhere because the appropriate controls would be in place.

However, significant regulatory barriers surrounding this approach still exist, which may impede sponsors' ability to implement. Notably, regulators require sponsors to identify all sites and site addresses as part of the application. If a site becomes mobile, either the definition of a site or reporting requirements for changing the location of a site will need revision [3]. Furthermore, regulators may need to re-envision the requirements for and the conduct of inspections.

Sponsors would need to invest upfront in a submission that included extensive data supporting their change (such as a technology transfer) by defining and comparing processes and systems in detail, as well as referencing supportive data in the form of prior knowledge. In the future, if changes were compared and deemed the same (low risk) or similar (low to moderate risk), a reduced data package could be submitted, ideally using a reduced reporting category, and without needing to meet with a health authority or use a PACMP.

Such subsequent postapproval submissions would only include process validation data and reduced analytical comparability data, with a commitment to provide stability data in an annual report or notification (see scenario 3 in Figure 1). Or, instead of manufacturing and testing three commercial lots to support a traditional process validation at a new site, a single commercial lot could be manufactured with a medium- to low-risk change implemented, as part of CPV (see scenario 4 in Figure 1), demonstrating that even with the change implemented, the process remains in a state of control because quality is built into the product [61] and the resulting product meets the quality target product profile (QTPP).

A site could initiate commercial production with the change implemented, and only batch analyses data could be submitted to health authorities after implementation in an annual report or notification. Of course, this would be contingent upon the comparisons made within that submission to the previously submitted processes, the capability (robustness) of the process, and justified applicability of the data sets (see scenario 5 in Figure 1).

The Impetus

Drug shortages continue to pose a challenge across the biopharmaceutical industry, resulting from delayed or discontinued manufacturing, or from patient demand exceeding available supply. Having more than one manufacturing site, or many manufacturing sites, as is the case with DM, with robust quality systems and supply chains in a sponsor's manufacturing network decreases the likelihood of a drug shortage by diversifying manufacturing locations to mitigate negative impact from natural disasters, for example, and by increasing likelihood of guaranteeing supply for and distribution to patients. Mitigating drug shortages should motivate sponsors and regulators alike to take full advantage of science- and risk-based approaches to expand manufacturing networks and available capacity, embrace emerging technologies to enable efficiencies and speed, and streamline health authority review durations; thereby, ensuring consistent, quality medicines for patients.

If regulators recognize that sponsors are "moving toward advanced manufacturing technologies, such as CM, for both small-molecule drugs and biological products... to improve the agility, flexibility, cost and robustness of manufacturing processes,"

and acknowledge that, "these technologies have great potential to accelerate new, more targeted therapies, enhance product quality and bolster stability in the... drug supply..." [51], then sponsors and regulators must embrace the submission and review of Module 3 content that is nontraditional but is science- and risk-based.

EMERGING REGULATORY INITIATIVES

The presented case studies demonstrate how existing regulations can be successfully applied to support unique manufacturing scenarios. However, adaptations to the current regulatory framework that specifically account for decentralized manufacturing models could streamline filing processes and establish a path for the implementation of novel technologies (see the enabling technologies and selected examples sections).

The use of science- and risk-based approaches and QbD should remain core tenets, but updates may help biopharmaceutical manufacturers better understand regulators' perspectives on facility registration, risk mitigation, and process controls in the context of DM, MM, and POC. Similarly, the regulatory framework should provide advice on managing inspection requirements, site addresses, and post-transport validation when DM or POC manufacturing sites are used. Regulators in some regions are moving toward creating tailored regulations and guidance for use with DM and POC manufacturing.

MHRA

In January 2023, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK announced its intent to develop a regulatory framework that supports POC manufacturing and issued a proposal detailing the agency's preliminary approach to POC regulation. Prior to the announcement, the MHRA worked with stakeholders to evaluate current challenges and the need to expand current regulations with additional supportive measures for POC manufacturing. The MHRA indicated that during this evaluation period, it had seen a variety of POC products, including cell and gene therapies, small molecules, and blood products [62].

The MHRA's framework proposal outlines the importance of establishing a control site, which will be designated in the marketing application as the establishment that upholds and oversees a core PQS for a distributed POC manufacturing network [62]. The control site is subject to inspection by the MHRA. It will be responsible for notifying the MHRA of significant manufacturing events and maintaining a master file. Along with the proposal, the MHRA has posed several questions to stakeholders to assess the need for and application of the proposed framework.

US FDA

Similarly, over the past decade, the US FDA has established a variety of initiatives and programs to enable novel manufacturing technologies. A recent example is the Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) initiative, which seeks to develop regulatory frameworks to support innovative manufacturing technologies [63]. One of the outcomes from this initiative was a discussion paper published in late 2022 to establish the FDA's terminology list corresponding to DM and POC, as well as to provide specific areas in which the regulatory framework may need to be adapted to better fit novel manufacturing paradigms [6].

The paper was published with the intent of seeking feedback from pharmaceutical developers to facilitate policy development on advanced manufacturing. The Omnibus Act, approved by the US Congress in December 2022, also influences advanced manufacturing by enabling the FDA to set advanced manufacturing and platform technology designations [64].

EMA

In the EU, one of the European Medicine Agency's (EMA's) documents outlines its strategic goal to enable the implementation of innovative manufacturing technologies [65] and to facilitate the formation of the Quality Innovation Group, which is tasked with conducting assessments, engaging with stakeholders, and issuing guidance documents on the topic of novel manufacturing technologies. The Quality Innovation Group has identified CM, DM, and POC manufacturing as key topics as part of the work plan [66].

Other Regions

Though other regions have these concepts on their radar, at the time of writing, not all health authorities have announced plans to issue specific guidance or regulation related to DM, POC, or MM.

ANTICIPATED FUTURE DEVELOPMENTS

Manufacturing and information processing technologies will continue to advance, expand, and influence our current ways of working to meet the needs of the evolving medical, biopharmaceutical, and regulatory environment. Under the framework established by ISPE's Pharma 4.0™ initiative, modern manufacturing facilities are anticipated to be increasingly digitized, autonomous, and risk based by design to allow for accelerated production while maintaining robust quality standards [5].

Smart Factories

As a key benefit, "smart" factories can consistently produce large volumes of high-quality data by leveraging automation, robotic support, remote monitoring capabilities, and cloud-based data exchange. In the context of DM and POC manufacturing, such tools can enable multiple, disparate sites to be controlled under a single harmonized quality and manufacturing system, with the ability to access data from anywhere via cloud-based enterprise systems. In this digitized environment, both regulatory submissions and health authority inspections can be made easier because data can be quickly harnessed and compared across multiple sites without the need to manually compile or physically visit individual locations.

Next-Generation Knowledge Management

With an increase in the overall volume of data generated, pharmaceutical manufacturers will also need to apply specific

solutions to help manage, store, parse, analyze, and mobilize data in the context of knowledge management [67]. Additionally, approaches in structured content management, as well as artificial intelligence (AI) and machine learning, can help make data accessible and usable in downstream applications, such as regulatory filings.

Although next-generation AI toolsets, such as text mining and natural language processing, can process unstructured data, having a structured data model helps AI tools work more efficiently and ensures the captured data is usable and kept in context with its source (see Figure 2). Layering AI tools, such as large language models (e.g., OpenAI's ChatGPT and others), on top of a structured data model can allow for further extensions in capabilities.

Cloud-Based Data Exchange

Cloud-based platforms will also help foster digital connectivity across physical locations. In particular, a cloud data exchange solution that connects sponsors and health authorities for real-time data exchange would help ease the burdens of continuous, high-volume data flow. Accumulus Synergy, a nonprofit founded in 2020, is developing a cloud platform with collaborative capabilities that can help reach this vision [67].

Dynamic Real-Time Approaches

Adapting more dynamic real-time approaches to analytical testing and feedback control, such as PAT, will become a crucial element of a cohesive control strategy that can be applied across different facility locations. In a future scenario, data could be streamed to a remote monitoring site and evaluated in real time, enabling feedback controls to ensure in-specification quality attributes and allow RTRT (see Figure 2). Additionally, manufacturers may be able to more rapidly adjust and modify conditions or procedures at one site based on testing outcomes from another site. Conversely, in the case that there is a failure in one site, AI learning may be leveraged to reduce or prevent the risk of failure in another site.

Simplified Technology Transfers

Extensive data collection, integration, and AI tools may also be used to model specific trends and develop predictive models that can inform the change management process. With necessary changes to the regulatory framework and an increased understanding of AI application and deployment, AI models could simplify the technology transfer process.

For example, if a sponsor uses a traditional approach for two or three initial technology transfers and adapts an AI algorithm to "learn" how to mitigate risks incurred during the process, subsequent technology transfers could be conducted under a "low" risk assessment assumption, as deep scientific understanding is significantly increased through AI learning during the previous technology transfer processes (see Figure 2) based on which changes are guided and executed.

AI Technology

There are multiple potential future applications of AI technology that can support more efficient technology transfer, scale-up, site monitoring, and regulatory submission processes (see Figure 2). AI can guide process improvement through iterative risk evaluation, wherein changes are made in response to an AI algorithm's readout, with data obtained using dynamic methods such as PAT. This can simplify future scale-up and technology transfer. Similarly, AI applications could be used as part of a remote monitoring strategy for multiple different decentralized sites, such as POD units. Finally, AI can assist with managing large volumes of data by enabling automated data parsing and sorting to streamline regulatory submission preparation.

Autonomous Production Systems

Some of the unique challenges of POC manufacturing, such as the training and qualification of on-site personnel, can be remedied by onboarding fully autonomous production systems. Healthcare workers are typically not trained in GMP manufacturing and are therefore not qualified to operate most POC facilities. If end user operation at the healthcare facility is extremely limited, fully autonomous production systems with virtual control may reduce the burden of personnel limitations.

Regulatory Considerations for AI Tools

Regulatory considerations for applications of AI and machine learning is an area of active discussion within several health authorities because greater understanding is needed before policy can be formally issued [66, 68]. AI has the potential to introduce significant complexity into manufacturing decision-making processes, which has downstream impact on regulatory assessment. As a result, a more realistic, near-term strategy may be to utilize AI to assist with data mining and text generation to streamline the regulatory submission authoring process, which will be necessary in the context of multiple sites.

CONCLUSION

Without a supportive regulatory framework, advances in biopharmaceutical manufacturing technology and innovative operating models will be impractical for sponsors to implement globally. Although technology and regulation have traditionally been on very different timelines, with technological innovation developing at an ever-increasing pace and the resulting regulations slow to follow on, they must ultimately evolve together to be maximally effective.

A balance must be reached to ensure that the biopharmaceutical industry can take full advantage of what the technologies have to offer and meet the challenges posed by the ever-changing supply and demand situation, as well as the evolving landscape in pharmaceutical manufacturing. Notably, patients are the ultimate benefactors of this evolution, as they will have more ready access to medicines globally.

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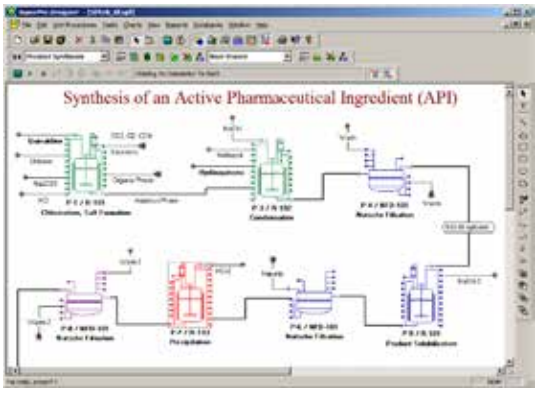

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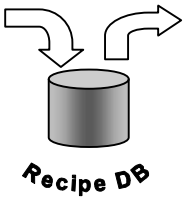

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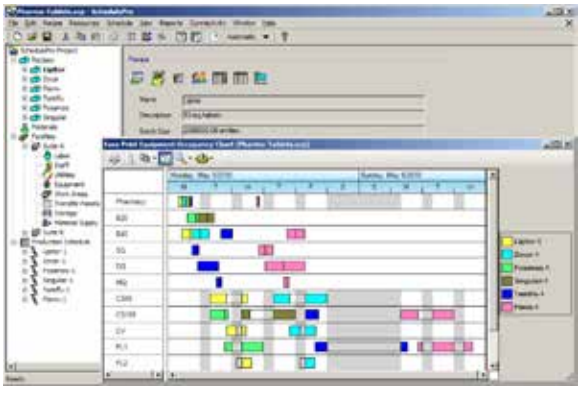
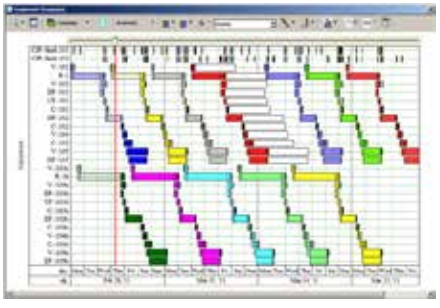


Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



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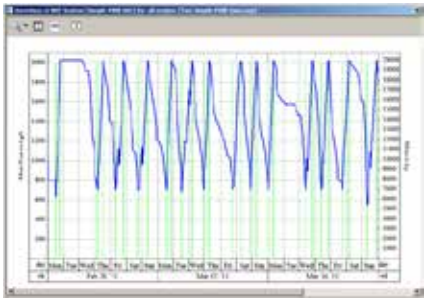

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SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size shared utilities, determine equipment requirements, reduce cycle times, and debottleneck facilities.

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NEW EU AI REGULATION AND *GAMP® 5*

By Anders Vidstrup

This article describes how *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* and related GAMP Good Practice Guides can be effectively applied to help meet the requirements of the proposed European Union (EU) artificial intelligence (AI) regulation for qualifying GxP-regulated systems employing AI and machine learning (ML).

On 21 April 2021, the EU Commission presented the long-awaited draft on the regulation of AI. The document is based on a number of reports from the EU Commission and aims to ensure citizens' trust in AI systems. The regulation is the first targeted legal regulation of AI. As such, it will have great significance in Europe and the rest of the world in relation to the development and use of AI. The AI regulation applies alongside the General Data Protection Regulation (GDPR), as systems must comply with both, e.g., when using personal data for training algorithms or when using AI systems for automatic decisions with legal effect for the data subjects [1].

The GAMP guidance may potentially prove useful for other areas and industries in supporting the quality assurance activities and methods described in the draft regulation, at the discretion of the organizations involved. *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* covers AI/ML components and their life cycles [2], and the *GAMP® RDI Good Practice Guide: Data Integrity by Design* covers the data life cycle aspects of such systems, which can help ensure data integrity, a key requirement for these types of applications [3].

DESCRIPTION OF THE AI REGULATION [1]

The AI regulation contains four types of regulations:

1. Prohibition of the use of certain AI systems (Article 5)
2. Special requirements for the use of AI systems that are considered to present a high risk (Articles 6–51)
3. Transparency requirements for AI systems interacting with humans (Article 52)
4. A framework for voluntary "codes of conduct" for AI systems that are not high-risk systems (Article 69)

Prohibited AI systems are ones that harm people physically or psychologically with subliminal techniques or by exploiting vulnerabilities, that implement "social score cards" by monitoring citizens, and that use special forms of facial recognition/personal recognition.

High-Risk Systems

The focus of the AI regulation is to regulate high-risk systems, which are defined as those within eight areas:

1. Biometric identification and categorization of natural persons
2. Management and operation of critical infrastructure
3. Education and vocational training
4. Employment, worker management, and access to self-employment
5. Access to and enjoyment of essential private services and public services and benefits
6. Law enforcement
7. Migration, asylum, and border control management
8. Administration of justice and democratic processes

For management and operation of critical infrastructure, this includes AI systems intended to be used as safety components in the management and operation of road traffic and the supply of water, gas, heating,

and electricity. For employment and worker management, this includes AI systems intended to be used for the recruitment or selection of natural persons, notably for advertising vacancies, screening or filtering applications, and evaluating candidates in the course of interviews or tests. For access to private and public services, this includes AI systems intended to be used to dispatch or to establish priority in the dispatching of emergency first response services, including by firefighters and those administering medical aid.

For these systems, for example, a risk management system and a quality assurance system must be established, just as requirements for human involvement, transparency, robustness, cybersecurity, and correctness must be established. This is where *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* [2] and the *GAMP® RDI Good Practice Guide: Data Integrity by Design* [3] can be useful. The *GAMP® 5* framework and other GAMP guides already contain strong and mature guidance on the establishment of quality assurance systems and risk management systems, and on ensuring the integrity of data, which is essential for robustness and correctness.

Appendices

Appendix D11 in *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* focuses on AI/ML [2]. It provides a basic understanding of AI, the use of static and dynamic ML subsystems in industry, and guidance on how to ensure compliant integration and fitness for use in a regulated environment. It also presents an overview of a risk-based, regulatory-compliant AI/ML life cycle framework that aligns with *GAMP® 5* principles and phases (concept, project, and operation).

It describes the importance of data integrity to the overall quality of AI/ML, in addition to presenting an understanding of inherent risks, and acknowledges the iterative nature of developing AI/ML as a subsystem within the overarching IT application and/or business solution, all in conjunction and support of good software quality engineering practices.

Appendix S1 in *GAMP® RDI Good Practice Guide: Data Integrity by Design* [3] examines the area of ML and the importance and implications of data integrity on the outcomes of what "machines" are able to process and/or learn from the data made available to them. Both Appendix D11 and Appendix S1 describe a life cycle approach, from concept to project (i.e., data modeling and evaluation) and operation, including deployment and continuous monitoring.

AI TECHNICAL DOCUMENTATION AND *GAMP® 5*

In *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* [2], Article 11(1) describes the technical documentation needed. It outlines that it shall contain at least the following information, as applicable to the relevant AI system, as shown in the following tables.

CONCLUSION

AI and ML are transforming the way in which industry is doing business and processing data. The pharmaceutical industry is

Table 1: Regulation of AI and corresponding *GAMP® 5* guidance that covers a general description of the AI system.

A General Description of the AI System, Including:	*GAMP® 5* Sections and Appendices that Support These Requirements
Its intended purpose, the person(s) developing the system, date, and system version	D6–System Descriptions
How the AI system interacts or can be used to interact with hardware or software not part of the AI system, where applicable	• D6–System Descriptions • D1–Specifying Requirements
Versions of relevant software or firmware and any requirement related to version update	D6–System Descriptions
Description of all forms in which the AI system is placed on the market or put into service	• **Not supported by *GAMP® 5*** • Partially covered in D11–Artificial Intelligence and Machine Learning (as part of concept phase)
Description of hardware on which AI system is intended to run	• D6–System Descriptions • D1–Specifying Requirements
Marking and internal layout of products when the AI system is a component of products, photographs, or illustrations showing external features	**Not supported by *GAMP® 5***
Use and installation instructions	• Main section chapter 6.1.3 • Main section chapter 7.12

Table 2: Regulation of AI and corresponding *GAMP® 5* guidance that covers a detailed description of the elements of the AI system and the process for its development.

A Detailed Description of the Elements of the AI system and the Process for Its Development, Including:	*GAMP® 5* Sections and Appendices that Support These Requirements
• Methods and steps performed for the AI system development • Third-party pretrained systems and tools • How third-party systems and tools have been used, integrated, or modified by the provider	• Main section chapter 3 and chapter 4 describe activities in general • D11–Artificial Intelligence and Machine Learning partially covers the pretraining system • The pretraining system could be described in a functional specification (Appendix D1) or partly in a validation plan (Appendix M1)
• System design specifications (general logic of the system and algorithms) • Key design choices (including rationale and assumptions) • Key design choices with regard to persons or groups of persons on which the system is intended to be used • Main classification choices • What the system is designed to optimize for and relevance of different parameters • Decisions about any possible tradeoff made regarding the technical solutions adopted to comply with the requirements set out in Title III, Chapter 2	• D1–Specifying Requirements (partly covered) • D11–Artificial Intelligence and Machine Learning covers main classification choices • S1–Artificial Intelligence: Machine Learning covers main classification choices
• Description of the system architecture, explaining how software components build on or feed into each other and integrate into the overall processing • Computational resources used to develop, train, test, and validate the AI system	D6–System Descriptions
• Data requirements (in terms of datasheets) describing the training methodologies, techniques, and data sets used • Data set provenance, scope, and main characteristics • How data was obtained and selected • Labeling procedures (e.g., for supervised learning) • Data cleaning methodologies (e.g., outlier detection)	• D11–Artificial Intelligence and Machine Learning • S1–Artificial Intelligence: Machine Learning
• Assessment of the human oversight measures needed in accordance with Article 14 • Assessment of the technical measures needed to facilitate the interpretation of the outputs of AI systems by the users, in accordance with Articles 13(3)(d)	• **Not directly covered by *GAMP® 5*** • D11–Artificial Intelligence and Machine Learning covers to some extent
• Detailed description of predetermined changes to the AI system • Detailed description of the AI system's performance • All relevant information related to the technical solutions adopted to ensure continuous compliance of the AI system with the relevant requirements set out in Title III, Chapter 2	• 08–Periodic Review • D6–System Descriptions • D11–Artificial Intelligence and Machine Learning
• Validation and testing procedures used • Information about the validation and testing data used and their main characteristics • Metrics used to measure accuracy, robustness, cybersecurity, and compliance with other relevant requirements set out in Title III, Chapter 2 • Potentially discriminatory impacts • Test logs and all test reports dated and signed by the responsible persons, including with regard to predetermined changes as referred to in the row above	• Main section chapter 7.10 (Testing) • D5–Testing of Computerized Systems • Main body section and M3–Science-based Quality Risk Management should be considered for challenge test

increasingly relying on such innovative technologies to automate many functions previously performed by humans. As computer systems become more integrated and datasets become more extensive, computer science is advancing our ability to learn from that data and draw conclusions.

Underlying algorithms are sophisticated enough to begin making robust decisions in the form of AI. The listed requirements in the draft regulation for developing and operating high-risk AI systems are all based on good engineering practice. Many activities in *GAMP® 5* and supporting guidance, like *GAMP® RDI Good*

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Table 3: Regulation of AI and corresponding *GAMP® 5* guidance that covers detailed information about monitoring, functioning, and controlling the AI system.

Detailed Information about Monitoring, Functioning, and Controlling the AI System, Including:	*GAMP® 5* Sections and Appendices that Support These Requirements
• Its capabilities and limitations in performance • Degrees of accuracy for specific persons or groups of persons on which the system is intended to be used • Overall expected level of accuracy in relation to its intended purpose • Foreseeable unintended outcomes and sources of risks to health and safety • Fundamental rights and discrimination in view of the system's intended purpose • Human oversight measures needed in accordance with Article 14 • Technical measures to facilitate interpretating the outputs • Specifications on input data, as appropriate	D11–Artificial Intelligence and Machine Learning
Detailed description of the risk management system in accordance with Article 9	• *GAMP® 5* main body section 5 (Quality Risk Management) • D11–Artificial Intelligence and Machine Learning (partially covered)
Description of any change made to the system through its life cycle	• 06–Operational Change and Configuration Management • 08–Periodic Review
• List of the harmonized standards applied in full or in part (the references of which have been published in the *Official Journal of the European Union*) • Where no such harmonized standards have been applied, a detailed description of the solutions adopted to meet the requirements set out in Title III, Chapter 2, including a list of other relevant standards and technical specifications applied	**Not covered or supported in *GAMP® 5***
Copy of the EU declaration of conformity	**Not covered or supported in *GAMP® 5***
Detailed description of the system in place to evaluate the AI system's performance in the postmarketing phase in accordance with Article 61, including the postmarketing monitoring plan referred to in Article 61(3)	• 08–Periodic Review • D11–Artificial Intelligence and Machine Learning (partly supported) • S1–Artificial Intelligence: Machine Learning (partly supported)

Practice Guide: Data Integrity by Design, are also based on good engineering practice and, as such, can serve as the basis for how to fulfill the listed requirements.

Even though high-risk AI systems are not evaluated as GxP systems, it will be beneficial to use the GAMP-based quality activities from the company's quality management system. *GAMP® 5 (Second Edition)* and related GAMP Good Practice Guides can be effectively applied to help meet the requirements of the proposed EU AI regulation for GxP-regulated systems employing AI/ML that fall under the scope of that regulation. GAMP guidance may also prove useful for any organization wishing to meet the quality assurance requirements of the draft regulation for other AI/ML systems.

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About the author

Anders Vidstrup is a Senior IT Quality subject matter expert at NNIT, working with quality aspects of computer-related systems. He is responsible for deliverables to pharmaceutical and financial customers. For the past 23 years, he's been involved in the qualification of process control systems (PCS) in a large plant for drug production, lab systems, and administrative GxP systems, including the full stack from infrastructure to application, both on-prem and cloud solutions. He represents the Danish Standardization Organization in International Standardization Organization on health informatics standards and AI. He has been a contributing writer for several GAMP Good Practice Guides and is Chair of the Cloud Community of Practice (CoP) and a member of the GAMP® Europe CoP Steering Committee. Anders has a background as a mechanical engineer and a graduate diploma in business administration. He joined ISPE in 2000.

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ENABLING GLOBAL PHARMA INNOVATION: Delivering for Patients

By Christopher Potter, PhD

ISPE has launched an important new initiative, "Enabling Global Pharma Innovation: Delivering for Patients," in support of the aspirations of many regulatory agencies globally to promote introduction of innovative pharmaceutical manufacturing.

It is incumbent for industry to modernize manufacturing processes to improve efficiency and increase confidence in quality assurance for the benefit of patients while introducing novel technology and modalities as the science advances. However, significant barriers exist for the global implementation of new, innovative technology for chemistry, manufacturing, and controls (CMC). Most important, the lack of global regulatory harmonization reduces incentives for industry to invest in these innovations, which, in many ways, limits access of safe, effective, and quality drug products to patients globally.

THE INITIATIVE

This initiative is consistent with ISPE's mission and vision and is aligned with the advancement of the Pharma 4.0™ program. The scope includes innovations in modalities, modes of delivery and administration of medicines, pharmaceutical manufacturing and analytical technology, and digital transformation.

A team of industry leaders with expertise in advancing innovative technology and products and with experience addressing regulatory divergence was assembled in late 2022. This ISPE team developed a comprehensive survey, with the objective of gathering data on the specific origins, extent, and magnitude of the challenges and barriers that limit or reduce the development and implementation of innovative technologies. The survey launched in April 2023, is still open, and can be found at https://ispe.org/initiatives/regulatory/enabling-global-pharmaceutical-innovation-delivering-patients

The survey consists of three parts, with the option to respond to all or any of the parts. The first is a list of questions requiring multiple-choice answers; the second requests brief answers to specific questions; and the third requests more detailed information and, where appropriate, examples of innovation challenges.

In addition, the team members intend to solicit responses from industry manufacturers, contract development and manufacturing organizations (CDOs and CMOs), material suppliers, equipment and facility engineers, and designers. Representatives from regulatory authorities are also encouraged to complete the survey. Results will be presented at meetings, summarized in blogs, and eventually issued in a report.

Data and information from the survey will be used to develop case studies and potential solutions that could serve as substrate for engagement with regulatory assessors and inspectors globally. A focus on the specific sources of challenges to innovation will encourage advancement of globally acceptable and enabling regulatory approaches and will reveal pragmatic opportunities and potential incentives to capitalize on stakeholders' commitment to innovation.

This article describes the goal of the initiative, characterizes the anticipated challenges to innovation, summarizes the industry's need to innovate, and discusses regulatory initiatives that are currently in progress, including learnings from the recent pandemic. In addition, this article provides an explanation of the purpose and expected outcomes from the survey, subsequent plans for communicating the results from the survey across ISPE, and development of concrete proposals to address the sources of challenges and barriers to innovation.

PROGRAM GOAL

The program's goal is to catalyze consistent and harmonized interpretation and implementation of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, with the intention of improving global patient access to innovative medicines and technology. Addressing divergence in global regulatory expectations is imperative to improve the advancement of pharmaceutical and technological innovation. Regulatory harmonization, which is fundamentally based on criteria described in ICH guidelines, depends on several pivotal objectives, such as:

- Leveraging relevant regulatory harmonization activities under consideration and convergent regulatory approaches in progress regionally
- Increasing the level of clarity and consistency in harmonized approaches that encourage and provide incentives for implementation of innovative technology for new, approved, and generic products
- Reinforcing globally harmonized implementation of science- and risk-based ICH guidelines that are functionally necessary to advance innovative technology and approaches like Pharma 4.0™, which requires a globally agreed-upon control strategy
- Contemporizing manufacturing technologies, especially those innovations currently supported by some local or regional regulatory authorities but not universally accepted by others
- Identifying sources of business as well as regulatory challenges that serve as barriers or create limitations in development and applicability of innovations across multiple therapeutic modalities; developing and implementing solutions to reduce or eliminate these challenges
- Encouraging and providing incentives for regulatory authorities to work together to accelerate adoption and implementation of ICH guidelines and other harmonization proposals, e.g., mutual recognition and reliance and collaboration and resource-sharing
- Assessing learnings from the pandemic with respect to the global regulatory and supply distribution experience, which can serve as a roadmap for improved implementation of innovative technology and can expedite increased patient access to medicines globally

Harmonization of global regulatory requirements has formally and informally progressed for more than 30 years under the ICH. ICH is committed "to achieve greater harmonisation worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner" [1].

Internationally, acceptable scientific guidelines—primarily applicable to commercial registration of new and generic drug products and drug substances—have dramatically improved regulatory alignment for many technical approaches focused on safety, efficacy, and quality of drug products. However, several published assessments and a large body of anecdotal examples indicate that implementation of many concepts described in ICH guidelines (i.e., a single global product control strategy) is not currently achievable [2].

Diverse regulatory expectations create additional burdens and challenges in carrying out continual improvement initiatives.

PROBLEM STATEMENT

Science- and risk-based approaches in pharmaceutical development were first explicitly described in ICH Q8 [3] and further elaborated in ICH Q9, Q10, and Q11 [4–6] as well as in Q12 [7] for postapproval changes. Conceptually, quality by design (QbD) is a prospective approach that increases process understanding, manufacturing robustness, and product knowledge to improve confidence in quality of pharmaceutical products.

However, during the last decade, industry has experienced a proliferation of regulatory divergence with respect to the interpretation and implementation of ICH guidelines (and control strategies) across geographic regions. Rather than the adoption of globally harmonized regulatory criteria, localized interpretations of ICH guidelines have resulted in widely different regulatory expectations, which have forced companies to adopt multiple control strategies for a single product using the same manufacturing process globally, or worse, diluted the control strategy toward the most conservatively harmonized common denominator.

This has created manufacturing and supply chain challenges and discouraged technical innovations that might otherwise provide increased quality assurance and expedite patient access to medicines globally, both at initial regulatory approval and for subsequent changes. These diverse regulatory expectations create additional burdens and challenges in carrying out continual improvement initiatives and, even the perception of divergence hinders innovation in product development and life cycle management while providing no improvement in product quality, safety, or efficacy. Global regulatory divergence has served as both a real and perceived barrier to develop innovative manufacturing technology, new medicinal modalities, and continual improvement initiatives that have, in some instances, created temporary drug shortages in some markets.

REGULATORY ACTIVITIES

Over recent years, several regulatory agencies have established initiatives to promote pharmaceutical manufacturing innovation.

To date, there remains no effective mechanism to obtain consistent, globally aligned regulatory assessment for innovative pharmaceutical technologies or modalities.

USA

The FDA established the Emerging Technology Program (ETP) in 2014 and has actively promoted the program [8]. In his keynote presentation at the 2022 ISPE Annual Meeting & Expo in Orlando, FL, Dr. Michael Kopcha, Director of the Office of Pharmaceutical Quality, emphasized the FDA's commitment to promoting advanced manufacturing. The Center for Drug Evaluation and Research (CDER) established the Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) initiative to prepare a regulatory framework to support the adoption of advanced manufacturing technologies that could bring benefits to patients [9].

The EU

The national competent authorities of the 27 EU member states, plus those of Iceland, Liechtenstein, and Norway, and the European Medicines Agency (EMA) released the "European Medicines Agencies Network Strategy to 2025" in 2020 [10]. Three of the six strategic focus areas are data analytics, digital tools and digital transformation, and innovation. In line with this strategy, the EMA established the Innovation Task Force (ITF), a multidisciplinary group that includes scientific, regulatory, and legal competences. It was set up to ensure coordination across the agency and to provide a forum for early dialogue with applicants on innovative aspects in medicines development [11].

The UK

The Medicines and Healthcare Products Regulatory Agency (MHRA) established the Innovation Office, which is open to ideas for innovative medicines, medical devices, and manufacturing processes [12].

Japan

The Pharmaceuticals and Medical Devices Agency (PMDA) has established the Innovative Manufacturing Technology Working Group (IMT–WG) with objectives to propose a new regulatory framework for the pharmaceutical quality control by the new technologies and to establish PMDA's perspective on the latest technologies of pharmaceutical quality control [13].

The Need for Global Focus

Although these regulator-sponsored initiatives represent opportunities to encourage and accommodate innovative technology, each is regionally focused. To date, there remains no effective mechanism to obtain consistent, globally aligned regulatory assessment for innovative pharmaceutical technologies or modalities. Investments in the development of these innovations are costly and frequently are technically and commercially risky. This is made even more true in the absence of a regulatory landscape that does not provide for the prospect of a single globally harmonized approval for the implementation of that innovative technology or modality.

Many leaders from regulatory authorities across the globe are beginning to appreciate these challenges and the lack of a globally harmonized regulatory incentive to motivate pharmaceutical innovation. The International Coalition of Medicines Regulatory Authorities (ICMRA), consisting of the heads of 30 medicine regulatory authorities, issued a policy statement in June 2021 recognizing "that pharmaceutical manufacturers seek agility to maintain robust supply chains and continually update manufacturing processes to incorporate changes and improvements as equipment ages, suppliers change, innovations are developed, and knowledge is gained [14]."

ICMRA goes on to state that it "recognizes that regulatory authorities can gain efficiencies by developing common procedures, guidelines, requirements, and interoperable infrastructure that would facilitate the timely sharing of information among regulators on changes occurring within the supply chain" [6].

ICMRA has established a pharmaceutical quality knowledge management system and, as part of this strategy, is commencing two pilot programs focusing on a) collaborative assessment, with initial focus on CMC postapproval changes and b) collaborative hybrid inspections. The overall aim of these pilots is to improve manufacturing capacity for production of critical medicines and to facilitate collaborative assessments and inspections by multiple regulatory authorities [15].

In addition, regulatory work-sharing programs have introduced opportunities for regulatory alignment across multiple regulatory authorities that could serve as models for implementation of global regulatory harmonization. Project Orbis was started in May 2019 by the FDA's Oncology Center of Excellence (OCE) to enable faster global access to cancer treatments. As of April 2023, there are eight countries involved: Australia, Brazil, Canada, Israel, Singapore, Switzerland, the UK, and the US [16]. The Access Consortium is a collaborative effort between Australia, Canada, Singapore, Switzerland, and the UK, all like-minded, medium-sized regulatory agencies [17].

LEARNINGS FROM THE COVID-19 PANDEMIC

In response to the magnitude and urgency of the COVID-19 pandemic, several opportunities emerged that could be adapted to

improve global convergence of regulatory alignment for the implementation of innovative technologies and modalities, including the following learnings:

- The implementation of parallel, rather than sequential, development in accordance with science- and risk-based approaches and effectively leveraging prior knowledge significantly accelerated the development of innovative products
- Increased collaboration between industry sponsors and regulatory authorities as well as collaboration among regulatory authorities enabled rapid approval of new applications, and applications for new manufacturing sites and manufacturing changes/optimizations that expedited global access to products
- The effective embrace of mutual reliance and mutual acceptance for both regulatory application reviews and inspections improved global access to products

INDUSTRY PUSH FOR INNOVATION

The pharmaceutical industry has continued to introduce innovative technologies and modalities despite the divergence in regulatory expectations. These include a) improved capability and efficiency in chromatographic separation technology for manufacture and purification of small and large molecules, b) the use of spectroscopic technologies that establish real-time release testing rather than conventional end product testing, and c) the adoption of agile manufacturing methodologies that increase flexibility through portability and modularization, and allow manufacturers to respond to patient needs on demand, offering a potential solution to enable timely access to critical medicines regionally.

Artificial intelligence (AI) and automation have also seen strong interest. This is evident from the deployment of AI and machine learning technologies to optimize manufacturing operations and processes, as well as the introduction of automation and robotics to improve operational consistency for manufacturing and analytics. Other examples include 3D printing of drug products, novel and improved devices and diagnostic tools, continuous process manufacturing, increased digitalization toward adaptive controls, and the development of innovative and patient-centric drug delivery and administration options.

These innovative technologies provide improvement to meet several important objectives:

- Increased product quality assurance
- Reliability and adaptability of supply chains and inventory management to accommodate global access to medicines
- Manufacturing and analytical efficiencies
- Continual improvement opportunities
- Product access by facilitating speed to market
- Introduction of process optimizations and new patient-centric dosage forms
- Introduction of new drug substance manufacturing technologies that are environmentally sustainable, use less energy, and produce less waste
- Seamless and integrated digital information flow up and down the supply chain operations

Industry investments in innovative technologies and modalities are incentivized by the ease with which they can be approved and implemented globally. Improving global regulatory alignment, harmonization, and collaboration are therefore critically important to motivating pharmaceutical innovation.

ISPE ACTIONS

To deliver this initiative, ISPE has assembled a multidisciplinary, multinational team of subject matter experts under the leadership of Roger Nosal, Principal Consultant with Roger Nosal PharmaCMC Regulatory Consultants. The team is sponsored by Tom Hartman, President and CEO of ISPE, reports to the Regulatory Steering Council, and currently consists of Roger Nosal as the project lead; Carol Winfield, Senior Director, Regulatory Operations, ISPE, as the Operational Project Manager; and Christopher Potter, PhD, CMC Pharmaceutical Consultant, as the Project Advisor. The team members are:

- Nina Cauchon, PhD, Director, Regulatory Affairs–CMC, Amgen Inc.
- David Churchward, Global Head Sterility Assurance, Cell and Gene Technologies, Lonza Biologics
- Jean François Duliere, Regulatory Advisor, ISPE
- John Lepore, PhD, Principal, JVL Phama Consulting LLC
- Maurice Parlane, Principal/Director, New Wayz Consulting Ltd./CBE Pty. Ltd.
- Alice Redmond, PhD, Chief Strategy Officer, CAI
- Greg Rullo, Senior Director, Regulatory Affairs–CMC, AstraZeneca
- Hirofumi Suzuki, PhD, Product Supply Japan, Head of Project Supply Coordination, Bayer Yakuhin Ltd.
- Tim J.N. Watson, PhD, Vice President–Head of CMC Regulatory Affairs, Gilead Sciences

Although the ultimate objective is to provide potential solutions to improve implementation of global regulatory expectations, this team will initially gather data to identify specific sources of industry and regulatory challenges to innovation. A survey has been designed to determine the extent and magnitude of challenges and barriers globally in developing and implementing innovative technologies. The survey was launched in late April 2023 and is open to both ISPE members and non-members.

SURVEY DESIGN

The survey is divided into three parts and all sections focus on the development and implementation of innovative technologies and modalities. Part 1 is a 10-question, multiple-choice inquiry that is intended to develop an understanding of the demographics and an overview of respondents' experience with the subject. Part 2 has short-answer questions that focus on eliciting increased granularity regarding respondents' experience. Part 3 offers the respondents the chance to provide anecdotal examples describing successful introduction of innovative technologies and/or challenges associated with developing and implementing innovative technologies and modalities.

There is an opportunity to provide contact details so that the team may follow up. Each part of the survey will be distributed through ISPE to members and other stakeholders throughout 2023. While responses to all three parts of the survey would be welcome, completion of part 1 will allow assessment of the magnitude of the concerns associated with barriers to innovation.

Case studies will be developed from the survey feedback with proposed solutions, which should support engagement with regulatory authorities globally. Results from each part will be presented periodically at ISPE meetings throughout 2023 and 2024. A final report will be provided as the basis for an ISPE workshop, with recommendations subsequently published in *Pharmaceutical Engineering* and other trade publications.

CONCLUSION

In response to the desire of both regulators and industry to introduce new and innovative technology and modalities and improve product quality assurance and access to medicines for patients globally, ISPE has launched the "Enabling Global Pharma Innovation: Delivering for Patients" initiative. A multidisciplinary, multinational project team has been assembled and early objectives have been identified.

The survey was launched in April 2023 to determine the extent and magnitude of the global challenges and barriers in developing and implementing innovative technologies. Data and information from the survey will be used to promote efforts to establish durable, globally harmonized regulatory approaches to effectively enable implementation, support continual improvement, and provide consistent guidance for innovative technologies.

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About the author

Christopher Potter, PhD, retired in 2007 and now performs CMC consultancy work and is an ISPE Advisor. Previously he worked at Beecham Research Laboratories and Sterling-Winthrop in pharmaceutical and analytical development management positions, focused on ethical and over-the-counter drug development. Chris also worked at ICI Pharmaceuticals, now AstraZeneca, as Manager of analytical development, R&D QA, and CMC project management groups, and as Director of external pharmaceutical programs with responsibility in both the UK and US. From 1996 to 2007, he was a member of the European Federation of Pharmaceutical Industries and Associations (EFPIA) ad hoc Quality Group, EFPIA topic leader for ICH Q6A and ICH Q4B, and led EFPIA's PAT Topic Group. He holds a degree in chemistry from the University of Exeter and a PhD in organic chemistry from Imperial College, London University. He has worked on many ISPE programs and has been an ISPE member since 2007.

Please send any questions regarding this initiative to Carol Winfield at **CWinfield@ispe.org**

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CATHERINE HALL

Catherine Hall is Chair of the Investigational Products, North America (IPNA) Community of Practice (CoP) Steering Committee and is one of the authors of the *ISPE Good Practice Guide: Investigational Medicinal Product Reverse Logistics – Good Returns and Reconciliation Practices*. She has been a member of ISPE for 18 years.

She is currently Vice President of Data and Quality at endpoint Clinical, an interactive response technology (IRT) systems and solutions provider that supports the life sciences industry and provides software that helps randomize patients, maintain confidentiality, and distribute clinical supplies for clinical trials. Catherine started her career as an academic scientist in molecular and cellular biology before finishing her MBA and transitioning into working with the pharmaceutical supply chain.

"I'm a biochemist by training and I've always had an interest in medicinal products and how they work. Before coming to endpoint, I worked for pharmaceutical companies for 20 years, mostly in clinical supply chain management. I enjoy learning about what is new on the horizon of medical research and what could bring help to patients and their families. Now, I get to be involved with hundreds of companies and have a part in bringing new medicines to market," Hall said.

She feels that IRT, though decades old, is an essential part of the clinical trial in phases two and three. "But we still need to bring technological solutions to other phases of development. The size of data is continually growing and it's getting to a point within a clinical trial that you need machines to evaluate the data to get some semblance of the results. I think naturally we need to be thinking about the role of artificial intelligence and machine learning and how it could help to support clinical trials and how they're conducted and analyzed in the future.

"We still do one clinical trial at a time, and we collect data every time on control patients taking placebos. If you look through the history of clinical research, do we really need more data on patients without treatment? Or can we use and reuse data from previous trials to help ensure that volunteers that come into clinical trials are getting the option of care that they're looking for and we are collecting data on the new drugs and not just on a condition that we already know a lot about? I really think as we move forward and think about technology, there will be a focus on standardizing the data and sharing it around the world."

Sharing is the focus of the podcast the IPNA CoP Steering Committee is currently working on. "One of the things that we've noticed within the committee over the last several years is that the big pharma companies have good communication amongst each other. But when you get to the mid and smaller companies, they don't really have that interaction. We want to give a face and a voice to all the leaders across our industry. What challenges are they facing? What innovations and solutions are they bringing to the table? We also want to explore what's going on at clinical sites, with patients and the suppliers supporting the trials."

In addition to her volunteer activities with ISPE, Catherine volunteers with Knitters for Knockers and is an advocate and educator for Tourette syndrome.

—Marcy Sanford, ISPE Publications Coordinator

HUBERTUS REHBAUM

Hubertus Rehbaum, PhD, is Chair of the Process Analytical Technology & Lifecycle Control Strategy (PAT-LCS) Community of Practice (CoP) Steering Committee. He's been a member of ISPE for eight years. He first became involved through the Germany/Austria/Switzerland (D/A/CH) Affiliate when he joined as an Emerging Leader and helped co-host events for the group, which he said helped him develop a wider view of what the pharmaceutical industry is about.

"The Emerging Leaders is a perfect platform to look outside your own box and work experience and learn about different opportunities. I graduated from university with a degree in electrical engineering and a PhD in applied computer science but at some point, I knew I wanted to go in a different direction. Participation in the ISPE Emerging Leaders program provided exposure to the areas I was curious about," Rehbaum said.

A resident of Germany, Rehbaum started his career at Ottobock, a leading company in prosthetics and orthotics. There he worked as a researcher on advanced hand prosthetics, developing algorithms to analyze multivariate muscle signals for intuitive control of the hand prosthesis. After earning his PhD, he became the head of research and development for L.B. Bohle, a technology company that develops and builds process equipment for the production of pharmaceutical products, especially oral solid dosage manufacturing.

In 2016 he started his own company, Dr. Rehbaum Technology Consulting GmbH. "I work with many different teams and customers in North and South America, Europe, and Asia. They all adhere to the same PAT requirement and regulations, but the way issues are being solved is very different among different cultures and companies, which makes my role very interesting. I've been able to get a wide view of how analytical problems are being solved, which is something I would not be able to experience if I was working for just one company. Sometimes there's not only one truth, but multiple ways that 'lead to Rome,' as they say, which is something that I was never able to experience before, and it's something that I really love about my work now."

Rehbaum says the PAT-LCS CoP has been a great way to bounce ideas off others and a place to go when seeking answers. "The CoP, especially the Steering Committee, is a community of friends and peers I can go to when I need to discuss ideas or talk through a solution to determine if it is a good approach." He and other members of the PAT-LCS CoP Steering Committee will be presenting "Application of PAT for Real-World GMP Operations" at the 2023 ISPE Annual Meeting & Expo in Las Vegas, Nevada, on Monday 16 October. The session will focus on best practices in the design, implementation, and operation of PAT for GMP operations, including operator skill set, team skills set, and IT infrastructure requirements to facilitate data management under GMP standards.

In addition to presenting at ISPE's Annual Meeting, Rehbaum is looking forward to meeting the students and recent graduates who have received travel grants from ISPE to attend the meeting. "It was great to see the students at this year's ISPE Europe Annual Conference in Amsterdam. There were 51 students and recent graduates from all over the world—not just Europe and US, but also Malaysia, the Philippines, and South America. The travel grants are a great opportunity and give students and recent graduates a chance to broaden their horizons and gain a deeper understanding of the pharmaceutical industry."

—Marcy Sanford, ISPE Publications Coordinator

2023 ISPE Annual Meeting & Expo Q&A

By Joydeep Ganguly

The Executive Chair for this year's Annual Meeting offers advice and shares what attendees can expect at the upcoming conference in Las Vegas, Nevada.

Ganguly is Annual Meeting Executive Chair for the 2023 ISPE Annual Meeting & Expo, held 15–18 October. He attended his first ISPE Conference in 2004 in Washington, DC, and has been an ISPE member since 2016. Ganguly has been a Facility of the Year Award (FOYA) judge and served on the Global Pharmaceutical Manufacturing Leadership Forum; he has also been published in *Pharmaceutical Engineering*® and was awarded the 2006 ISPE Roger F. Sherman Article of the Year Award.

Why Did You Volunteer to Be Executive Chair?

ISPE's Annual Meeting & Expo is an amazing curation of the industry's top minds within the operations space. As the world around us is changing and industry imperatives are evolving, I was intrigued by the opportunity to work with ISPE and the planning committee to develop an agenda that focused on two important items: a futuristic view of where operations, engineering, and technology are heading and to ground the conference in a real-world, practitioner-led agenda that people would find compelling. We have put together a conference that brings us closer to science and patients, includes topics that are promising to be constructive disruptors in our industry, and stays true to what consistently makes this conference special—a real-world focus.

In addition, this gave me a once-in-a-lifetime opportunity to get a front seat to the entire gamut of topics that were relevant, and the chance to review submissions that are defining the standards within our industry. So selfishly, this was a tremendous learning opportunity for me to benefit from the best of the industry.

What Are the Top Three Reasons You Would Tell Someone They Should Attend This Conference?

There are many reasons to attend this year's conference. There's a broad agenda that caters to every aspect of pharmaceutical operations, delivered by industry leaders that have shaped where we are today. The conference offers the chance to network with a peer circle that represents every part of the value spectrum within our industry. The agenda is cutting edge: It is not a rehash of topics we've heard, but truly a unique point of view on topics like modernization and digital and operational excellence, all through the eyes of experts that have a practitioner vantage point.

Any Advice for Someone Who Has Never Been to an ISPE Conference?

Learn and network. Take the time to not only listen to sessions, but also to network. Some of the most critical value I've gained from this conference has been in offline discussions with leaders and post-conference connections. Some of the projects that we've seen the greatest value from in my company and within my function started after a random conversation with a thought leader within a space I had little domain depth. That is the beauty of this conference: it creates an opportunity to connect with thought leaders and partners in a very organic manner.

What Are You Most Looking Forward to at the Conference?

In addition to attending some amazing sessions and keynotes, I am really interested in interacting with my peers.

Research Panel

I get the privilege of moderating a panel with Flavius Martin, who heads up worldwide research for Gilead Sciences, and I know he will share an interesting perspective on how, as a profession, we can add more value to the overall scientific ambitions within the industry.

Networking

I am really looking forward to connecting with colleagues, learning how different sectors within our industry are evolving, and hearing how peer organizations are continuing to redefine value.

The Next Generation of Leaders

I also spend a lot of time working with ISPE on emerging leader development, diversity internship sponsorships, and workforce of the future initiatives, so I am also looking forward to hearing about novel models in the space and learning from other companies and organizations on how they are investing in the next generation of leaders.

Why Do You Think Professional Development Is Important? What Professional Development Opportunities Are Available at the Conference?

Professional development is the foundation to our culture of continuous learning. If one aligns on the tenet that people are the

biggest asset within an organization, then investment in people through professional development opportunities is the surest and fastest way to create a culture of excellence. In my view, investment in professional development is how we continue to outinnovate problems, redefine innovation standards, and create value. As an industry that is very lucky to have a patient at the end of our supply chain, that value and innovation carries much meaning. In that sense, I see professional development as a leadership commitment—to ourselves and to our industry.

There are many professional development opportunities at the conference—from formal training sessions to industry-expert discussions to networking. This is also a great opportunity to find mentors in the industry. In fact, one of my first mentors was someone I met at a conference, who went on to inform multiple career decisions I made.

Why Do You Enjoy Being a Member of ISPE?

ISPE has been an invaluable resource for me. In the earlier years of my career, the Society served as an education portal, providing access to thought leaders and a network of colleagues who shaped my way of thinking. Eventually, as I began contributing more to conferences and forums, ISPE afforded me a platform to vet, discuss, and stress-test ideas that needed critical peer review.

As we now enter a new era—technologically and socially—I continue to be impressed by the efforts of ISPE to drive discussions and plans to inspire the next generation. ISPE and its foundation are doing important work to further inclusion and diversity efforts within our profession. It has informed the way I look at hiring, retaining, and developing talent within my own team and has created a greater sense of resolve to ensure our profession continues to find ways to lead in this space.

For more information or to register, visit ISPE.org/conferences/2023-annual-meeting-expo

About the author

Joydeep Ganguly is Senior Vice President, Global Operations, Gilead Sciences, responsible for several strategic functions, including corporate engineering and operations, capital planning, risk management, and the program management office. He serves as the company's Chief Sustainability Officer, leading environmental sustainability efforts, and oversees footprint strategy and corporate real estate. Previously, he spent 10 years at Biogen in executive positions of increasing responsibility in technical operations, manufacturing, and supply chain. He is on the Board of Directors of the Bay Area Council, BioCom, North Carolina State University's Supply Chain Research Consortium, and the Gilead Foundation. He has published in areas of bioprocess optimization, supply chain transformation, and advanced process control. He was recognized by the National Diversity Council as a Top 50 Diverse Leader in California, and as a top three industry leader in climate science risk management. He holds an MS in electrical engineering, an MBA, and a master's degree in healthcare management.

ISPE Initiatives Provide Guidance on Medicines Supply

ISPE task teams created reports and a model to examine the challenges surrounding drug shortages, emergency preparedness, and the supply chain of active pharmaceutical ingredients (APIs). This article outlines these initiatives.

2023 ISPE DRUG SHORTAGES PREVENTION MODEL

The 2023 ISPE Drug Shortages Prevention Model serves as a guide to help prevent drug shortages by providing quality, regulatory, and technical recommendations for the pharmaceutical manufacturing industry. The ISPE Drug Shortages Team developed the model as a follow-up to the ISPE Drug Shortages Prevention Plan that was released in 2014. The model provides expanded guidance that reflects the new insight and best practices that have emerged in the past several years.

"With the COVID-19 pandemic, various natural disasters, and other unforeseen large-scale events, the importance of ensuring drug supply chain has never been more apparent," said Tom Hartman, President and CEO of ISPE. "The Drug Shortages Prevention Model is a crucial step forward in ensuring that patients have access to the medicines they need. By providing guidance for manufacturers to prevent and mitigate potential shortages, the model will improve patient access to life-sustaining medicines and the reliability of supply."

The Drug Shortages Prevention Model describes three foundational areas for accountability: quality and manufacturing maturity, regulatory, and technology and innovation. The three areas cover 12 performance domains:

- Pharmaceutical quality system
- Cultural excellence
- Workforce capability
- Supply and distribution resilience
- Risk management planning
- Data analytics
- Advanced technology
- Digital solutions
- Sustainability
- Life cycle management
- Regulatory execution
- Evolving regulations

"If companies want to ensure they are prepared to avoid drug shortages whenever possible, they should strive to excel in each of the foundational performance domains outlined in the model," said Diane L. Hustead, Executive Director, Regulatory Affairs, Merck & Co., Inc., and Chair of the ISPE Drug Shortages Team. "Developing and implementing robust drug shortage prevention planning involves risk management at organizational, operational, and product-specific levels. It is truly an enterprise-wide endeavor."

The ISPE Drug Shortages Prevention Model is available for download at ISPE.org/publications/guidance-documents/2023-ispe-drug-shortages-prevention-model

REPORT ON ISPE WORK TO SUPPORT ESTABLISHMENT OF THE EUROPEAN UNION HEALTH EMERGENCY PREPAREDNESS AND RESPONSE AUTHORITY (HERA)

The EU HERA was launched as a new European Commission Directorate-General with a mission to prevent, detect, and rapidly respond to health emergencies. As part of the preparation for this new authority, the European Health and Digital Executive Agency (HaDEA) selected McKinsey & Company to lead two assessments and studies. McKinsey & Company then engaged ISPE to provide technical and regulatory expertise and advice on chemistry, manufacturing, and control aspects of manufacture and supply in two workstreams: stockpiling of antimicrobial resistance medical countermeasures and flexible manufacturing and innovation.

"ISPE put together a multidisciplinary team that included experts from Roche, Novartis, Merck & Co., Merck KGaA Darmstadt, Gilead, and others to take on the project," said Hartman. "We were very glad to apply our expertise for these particular workstreams by providing much-needed input and raising the right questions to ensure a diversity of perspectives."

The objective of the stockpiling workstream was to develop a feasibility assessment on stockpiling of countermeasures in antimicrobial resistance. For this workstream, ISPE contributed subject matter experts for two virtual workshops with follow-up one-to-one discussions. The workshops covered options for stockpiling, needs, and availability in the EU, as well as regulatory issues, appropriate funding mechanisms, and operational deployment issues.

For the flexible manufacturing workstream, ISPE conducted an anonymous response survey of its members and other industry professionals to better understand opportunities for flexible

manufacturing of therapeutic APIs and associated drug products to assist with alleviating drug shortages.

The report details inputs and outputs from the workshops and the survey results. "This engagement highlights the technical leadership and bench strengths of ISPE that is built on our 22,000-plus members' knowledge and commitment to assure reliable delivery of quality medicines to patients worldwide," said Georg Singewald, PhD, Senior Vice President, Global Head Engineering, MSAT, and Sustainability, F. Hoffmann-LaRoche AG, ISPE Project Steering Team Member. "We remain committed to providing support for major regulatory initiatives with development, manufacturing, and supply chain knowledge."

INCREASING DOMESTIC RESILIENCY IN THE SUPPLY OF ESSENTIAL ACTIVE PHARMACEUTICAL INGREDIENTS

This report was produced by ISPE in 2020 in response to a request from the US Department of Air Force Acquisition COVID-19 Task Force (DAF ACT) to advise on regulatory, technical, and workforce elements favorable to creating a more robust and sustainable domestic pharmaceutical manufacturing base for active pharmaceutical ingredients (APIs). The report lays out technical, regulatory, and workforce changes that stakeholders in any country or region could consider to reduce the risks of API shortages and meet market demands for essential medicines, especially during pandemics and other emergencies.

> "With the COVID-19 pandemic, various natural disasters, and other unforeseen large-scale events, the importance of ensuring drug supply chain has never been more apparent."

ISPE has bundled the reports in one download in keeping with its vision and mission and to provide solutions to complex pharmaceutical industry challenges and enhance efforts to develop, manufacture, and reliably deliver quality medicines to patients.

The reports can be downloaded at ISPE.org/publications/guidance-documents/ispe-readiness-report-bundle

Meet the ISPE STAFF

CAROL WINFIELD

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Carol Winfield, Senior Director Regulatory Operations.

Tell us about your role at ISPE: What do you do each day?

I spend most of my time working with the ISPE volunteers in the regulatory space. We have 19 committees, councils, and working groups that are doing incredible work bringing visibility to the industry's regulatory challenges and developing solutions that are delivered through ISPE content outlets: webinars, PE magazine articles, iSpeak blog posts, training materials, conference sessions, and ISPE Guidance Documents. My department also serves as a point of contact for health authorities, facilitating the flow of information between ISPE members and global regulators, for example through commentary on draft or consultation documents.

What do you love about your job?

I love working with and learning from our volunteers, who are some of the most interesting and dedicated people I've even known. I'm constantly amazed and humbled by their passion and commitment to making a positive impact in the industry and its ability to improve patients' lives. I feel fortunate to be in a position where I can help bring our members and global regulators together in settings where they can share knowledge to achieve common goals.

What do you like to do when you are not at work?

I transferred from ISPE's Tampa, Florida, office to the office in Bethesda, Maryland, in 2015, and my husband and I are still playing tourists in our "new" backyard. We particularly enjoy exploring the historical areas on Maryland's Eastern Shore and around the Chesapeake Bay.

2023 ISPE Aseptic Conference Regulatory Panel

By Jörg Zimmermann

On 7 March 2023, ISPE concluded the 2023 ISPE Aseptic Conference with a regulatory panel question and answer session. Attendees were invited to submit questions to the FDA representatives. This article offers highlights from the discussion.

At this year's session, most questions focused on technical pharmaceutical queries related to sterile products, whereas last year's panel had a lot of questions around audit practices during the pandemic and learnings from virtual and hybrid inspections. The insightful questions and open discussion made for a very successful session, and participants went home with information that will help them in their jobs.

A highlight of the session was the mutual praise from industry and regulators on how well the two parties worked together during the pandemic to bring vaccines and drugs to the patients in record time. Please note that views expressed by the panelists are not necessarily representative of the position of the FDA, and that questions and responses are lightly edited for clarity. A more comprehensive write-up can be found at ispe.org.

The FDA representatives in this panel were:

- Laura Fontan, Consumer Safety Officer, Center for Biologics Evaluation and Research (CBER)
- Sandra Boyd, Drug National Expert, Office of Regulatory Affairs (ORA)
- Brooke Higgins, Senior Policy Advisor for the Global Compliance Branch, Center for Drug Evaluation and Research (CDER)
- Rick Friedman, Deputy Director, Office of Manufacturing Quality, CDER

First air refers to the filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone. We hear people discuss the concept of second air. Do you align the phrase with the potential to add contamination?

Rick Friedman

I don't think many of us would want to subscribe to the concept of second air as appropriate. The standard is first air, and that means that there is no major blockage of air that would cause a perturbance, or disruption of air, and special attention should be afforded to the area of exposed sterile vials, syringe barrels, or bags. This needs to be demonstrated in the smoke study qualifications. The bottom line is that aseptic production equipment should be designed well, and other than machine components that are absolutely necessary, such as filling nozzles and stopper placement equipment, there shouldn't be any things that are directly above the product.

How will the FDA use Annex 1 in its final version?

Rick Friedman

Annex 1 is aligned and in harmony with the FDA's guidance for aseptic processing from 2004. The FDA has been involved in the development of the final version of Annex 1 via PIC/S (Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme). The FDA's guidance has different topics and details in it that are additive to Annex 1, but they are compatible. The FDA's guidance was written to last for a long time without being overly prescriptive. We describe the principles that facilitate voluntary compliance by the industry. Although local policies are in general alignment with PIC/S guidelines, there are some aspects that are additive in the EU, Australian, and other PIC/S member local guidelines on various topics.

With the mutual recognition agreement between the EMA [European Medicines Agency] and the FDA, do you think the FDA will also expect PUPSIT [pre-use post-sterilization integrity testing] for products released to the US?

Brooke Higgins

Our guidance does say that integrity testing can be performed prior to processing and that it should be routinely performed post use. It is similar to the language in Annex 1, which indicates that pre- and post-use testing should be done and then you can eliminate the pre-use test with risk assessment. Our guidance might not be identically worded to Annex 1, but it is equivalent and aligned.

If a fully automated process with a gloveless isolator does not require operator intervention in the critical zones, could that filling machine potentially be placed in a grade D or even less stringent room?

Laura Fontan

You must consider your sterile core where your filling is happening. Even though it's operating closed, you're going to need to open it for any maintenance procedures, for any preparation procedures, for any cleaning procedures, and every time you're setting it up for another filling process. So, you want that sterile core protected. You want it in a higher grade than a D because you don't want to impact the cleanliness of that sterile core in any operations that you need to do when it's open. You want the surroundings as clean as possible. We would not recommend a D or less stringent room for this kind of operation.

What are the most common observations in the past year, and how should a company respond to them?

Sandra Boyd

For me, the two most common observations are not having the data to support your room classifications. During inspections, I find beautifully written reports that are delightful to read. However, I'm always going to look at the data to support the classifications justified by those reports and that's where I'll find problems. There is no raw data to support the claims made in those reports. The second most common observation I find is media fills are not representative of routine manufacturing. Whether it's not documenting all the interventions during routine production so it is unknown how many should actually be done during a media fill or not trending interventions, the interventions performed during a media fill are not representative of the production process.

Laura Fontan

First, I've seen a lot of procedures that are either inaccurate or they're lacking the detail for production to perform their tasks correctly and consistently. Another one is that qualifications and validation reports and the data from the qualification don't get transferred into the process parameters or into the procedures to represent the way that the system was validated. Whether it's cleaning validation, autoclave validation, or disinfectant efficacy qualifications, they don't get transferred over into the procedures to get executed the way that they were validated.

Brooke Higgins

We are seeing a lot of issues with smoke studies. There are deficient air flow patterns that are obvious to us when we're watching the videos that are not being caught by the firms. Another area is the design of filling lines, especially older lines, and they are so difficult to work with. When you respond to our observations, we want to see a robust, comprehensive, systemic response—not a narrow response that focuses only on the specific examples cited on the FDA 483.

> A highlight of the session was the mutual praise from industry and regulators on how well the two parties worked together during the pandemic to bring vaccines and drugs to the patients in record time.

For example, there is an issue with one investigation. The company opened up that one investigation again, but they may need to expand their review to their full investigation system and consider all of the equipment that might be similar to the one piece that we had an issue with or all media fills—not just the one that we found an issue with—and then provide supporting evidence for commitments. Finally, there is the topic of time frames: When are you going to implement some of the corrective actions, and what are you going to do in the meantime?

How often should gloves for RABS [restricted-access barrier systems] be autoclaved?

Laura Fontan

You should look at the frequency based on your processing durations and how you are using the gloves. Check what the manufacturer recommends, because some gloves have a certain number of qualified autoclave cycles. What I would typically do is look at the firm's program of how they are autoclaving or treating their gloves and see what their use is, how their campaign manufacturing is, and see what their rationale is behind supporting their program for autoclaving their gloves.

With the US being a member of PIC/S, are products manufactured and marketed in the US required to meet Annex 1?

Rick Friedman

PIC/S membership is extremely valuable, as it actively supports convergence on inspector training. Besides convergence on inspection practices through shared training, there are additional benefits from policy engagement that lead to aligned thinking. The regulators weren't talking to each other en masse through any formal mechanism before we started working with PIC/S. I

mentioned already that there is the question of sovereign policies and local things. But PIC/S provides policies that are authoritative, and they do generally provide strong baseline standards that we refer to in our regulatory work.

The Emergency Use Authorization approval for the COVID-19 vaccines was a major success. Can the FDA adopt principles of how the EUA was implemented to expedite approval of drugs?

Laura Fontan

The agency was working on all parts of the approval process in parallel, the same as industry. And so instead of all the different steps being branched out and one after another, they were stacked and in parallel, which helped industry accelerate the development of the COVID-19 vaccines. We also stacked our review, looking at the use authorization for the vaccines, and we stacked it with multiple resources we borrowed from other parts of the agency.

This meant that there were other drugs and other applications that we put on the back burner because we put all our resources into the COVID-19 vaccine approval or authorization and then approval. This was a process that was justified for this health emergency, and we would not be able to do it on all drug applications. It was quite an experience and an amazing effort at the agency on all levels of management. But no, not doable under normal circumstances.

For indirect contact parts, is it necessary to employ sterilization? There are lines with no autoclave. Is there a way to accept decontamination with bioburden assessment and robust pre-cleaning? That is, if you can remove the parts.

Sandra Boyd

You should autoclave the contact parts like guard rails. If they're removable, we would want to see them autoclaved. I am curious as to why there are sites with no autoclave. I would expect if you can take format parts apart, you will autoclave it.

For gloveless Isolators, is it okay to omit contact plate monitoring?

Brooke Higgins

No, we would recommend that end-of-campaign monitoring should be incorporated.

How often should a disinfectant efficacy program be reevaluated and what principles are most commonly missed when creating a program?

Laura Fontan

You would want to reevaluate your disinfectant efficacy program if your facility isolates have changed. You also would want to reevaluate your program if you are adding or changing any cleaning agents. The part that is most commonly missed when we are looking at a disinfectant efficacy program and when we're looking at the qualification of the cleaning agents is that the different contact surfaces in the facility are not always included. Sometimes we see very common surfaces missing from the studies, like stainless steel.

My question is about gloveless isolators specifically and the inspection history there. Have you seen any observations with these closed systems that you would not have seen with a more traditional isolator with gloves on it? Or alternatively, is there anything that you specifically look for when you're inspecting a facility or reviewing a product that uses a closed gloveless isolator versus a more traditional system?

Rick Friedman

It's more the same in terms of the basic cGMP requirements. There might be some shift in our critical control point mindset in terms of what to cover; for example, in terms of, robotic arms maintenance, precision, maintaining the system as closed, mechanical system integrity, automation algorithms, IT software, and so on. But it's still aseptic processing. It just gets more into the realms of digitization and automation.

This is more of a compliment to the nonbureaucratic approach that the regulators took during the pandemic. I think you did a good job. Thank you. And if the vaccine industry does not win the Nobel Peace Prize, there's something wrong with the prize.

Rick Friedman

On behalf of everyone at the FDA, we appreciate that acknowledgement. Thank you.

It is amazing how fast the industry came up with the mRNA vaccines and other therapeutics. Within a year or so, industry and regulators were able to support the deployment of vaccines and therapeutics that literally saved tens of millions of lives around the world. Kudos to the industry for your brilliant accomplishments during extremely challenging times.

Acknowledgements

ISPE thanks the panelists for their open discussion of audience questions. We are looking forward to the next regulatory panel at the 2024 ISPE Aseptic Conference in Vienna, Austria, on 12–13 March. For more information, please visit ispe.org/conferences

About the author

Jörg Zimmermann is Vice President of External Affairs for Vetter Pharma Fertigung GmbH & Co. KG, Ravensburg, Germany, where he manages relationships with regulatory agencies, professional organizations, and other partners in the pharmaceutical industry. Before this role, he was responsible for Vetter Development Service, which includes manufacturing science and process development, technology and process transfers, project and service analytics, and drug delivery systems. He was Production Manager before becoming Director of Production of Vetter's production site at Lake Constance. Within Vetter, Jörg has held various positions in process implementation, new product introduction, and lyophilization process development. He has volunteered as conference chair, track leader, and speaker at conferences by ISPE, PDA, and Concept Heidelberg. In 2016, Jörg was elected to the ISPE International Board of Directors and previously served as Chair. Jörg studied pharmacy in Freiburg, Germany, and Cardiff, Wales, and is a registered pharmacist. He has been an ISPE member since 2006.

INDUSTRY PANEL ON ANNEX 1 IMPLEMENTATION STRATEGIES

By Randolph Fillmore

Annex 1, the European Union's revised GMP requirements for the manufacturing of sterile medicinal products, will take effect on 25 August 2023. In this panel, experts involved in industry's commenting of the draft versions of Annex 1 offered background information on how the document was developed and answered questions on its implementation.

Annex 1 will also be adopted by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the World Health Organization (WHO) and the requirements will become global. However, companies will have to start preparing for implementation immediately and key questions need answers. Nidhi C. Shah, Director Aseptic Processing SME at Sanofi Pasteur, moderated the panel "Annex 1 Implementation Strategies" at the 2023 ISPE Aseptic Conference in Bethesda, Maryland. The panelists were:

- Massimiliano Cesarini, Managing Director – Pharma, Omnia Technologies
- Richard Denk, Senior Consultant, Aseptic Processing and Containment, SKAN AG
- Christa B. Myers, Senior Fellow, Aseptic and Sterile Products, Vertical Market Leader, CRB
- Johannes M. Rauschnabel, PhD, Director, Advanced Technology Development and Innovation, Syntegon Technology GmbH
- Jörg Zimmermann, Vice President, Vetter Development Service, External Affairs, Vetter Pharma-Fertigung GmbH & Co.

What is a good concept for introducing a contamination control strategy [CCS]?

Christa B. Myers

Myers responded that most elements of a CCS have been there, but Annex 1 is now asking for an overarching strategy for contamination control strategy, written down in a document. This systematic approach should include a description of all measures taken to avoid microbial, endotoxin, and particle contamination.

"This question has been answered in almost all sessions today, and the answers have always been about airflows, room pressurization, and cleaning protocols," she said. "Annex 1 is just a little bit more prescriptive. The regulation now tells you what is needed, and which chapter covers it. I see it when people are doing gap assessments: there is almost a list they can go through to see what they are missing in CCS, from operators to cross-contamination from products. With CCS we have all the elements, while QRM is the basis."

What different isolator technologies exist, and which cleanroom zone can be used according to Annex 1?

Richard Denk

Denk said that Annex 1 describes two different types of isolator technologies: opened and closed. Open isolators have mouseholes for feeding containers like vials continuously or semi-continuously in and/or out. Open isolators can be placed in a class C environment. Closed isolators have no mouseholes and work with material transfer locks like with hydrogen peroxide decontamination or RTPs and can be placed in class D environment according to Annex 1. "With both isolator types, humans have no direct access to critical aseptic operations," he said.

Is RABS [restricted access barrier system] retrofit on existing filling lines possible?

Jörg Zimmermann

Zimmermann stated that RABS retrofits are possible, but not for all lines. "We've done it in our company for several lines. The key in operations is to have the doors closed during setup and operations: if doors are opened, we stop the batch," he said. "There was a nice definition of active/passive, open/closed RABS in the draft glossary. They took that out of Annex 1, but it might have helped us."

Christa B. Myers

Myers emphasized that for RABS and isolators, the operation is as important as the design and build. "They are not just the magic box," she said. "They are a fully integrated system."

Johannes M. Rauschnabel

Rauschnabel said that Annex 1 seeks to "get humans out of the process as much as possible."

What is the right material transfer system from a Grade C/D environment into Grade A?

Johannes M. Rauschnabel

Rauschnabel said that it was common to have pallets in the isolator fill suite, but this is changing with Annex 1 because pallet disinfection is a challenge. "For a room at minimum Grade C, people have to depalletize things: That is a change coming and that will require new handling and transfer equipment."

Richard Denk

Denk said that material transfer should always be unidirectional from a lower cleanroom class to a higher cleanroom class. There are validated systems on the market, as already mentioned: material airlocks, e-beam, or rapid transfer ports. Denk stated that in Europe, it was common practice to have open isolators in class D environments with appropriate material transfers. "Annex 1 is now demanding class C background for open isolators and this change will require an upgraded cleanroom design."

What is important to consider when working with high potency products in terms of airflow, and what is the history of 0.45 meters per second airflow in cleanrooms?

Johannes M. Rauschnabel

Rauschnabel said that although proper airflow at the working position should be set at 90 feet per minute, the draft version of Annex 1 said *at working height*. "I'm glad they took that out and put in 'working position,'" he commented, stating airflow should be set according to ISO 14644 (150 to 300 mm from the entry plane) and measured "where working takes place."

At 0.45 meters per second (m/s) at working height, the airflow can create turbulences that increase the risk of contaminating the product. He told attendees that the ISPE Germany/Austria/Switzerland (D/A/CH) Community of Practice for Aseptic Processing has generated data on this issue. (See "Air Speed Qualification: At Working Position or Working Level?" on page 34.)

Jörg Zimmermann

Zimmermann offered historical background on cleanroom airflow speed, noting that the 90 feet per second (0.45 m/s) principle came from the nuclear industry in the 1960s, and relied on the work of Willis Whitfield, the inventor of the modern cleanroom. Speeds set above 0.45 m/s caused cleanroom fans to be too loud and created an uncomfortable draft for people working in cleanrooms. It was finally established that 0.45 m/s was a more comfortable airflow for working in and that speed became part of ISO.

The session ended with questions from attendees and back-and-forth discussion between the floor and panelists regarding some of the finer points of and pros and cons of pre-use post-sterilization integrity testing (PUPSIT).

Randolph Fillmore is the director of Florida Science Communications, Inc. He has a BS in Anthropology, an MA in Medical Anthropology, and an MA in Journalism. He has written on health care and health care policy, medical research, pharmaceutical and medical device regulation, public health, biology, chemistry, physics, pharmacy, and the social sciences. Formerly, he was employed as a science writer at the Johns Hopkins University School of Public Health and later at the University of Maryland Baltimore School of Pharmacy. He has been a member of the National Association of Science Writers since 1994.

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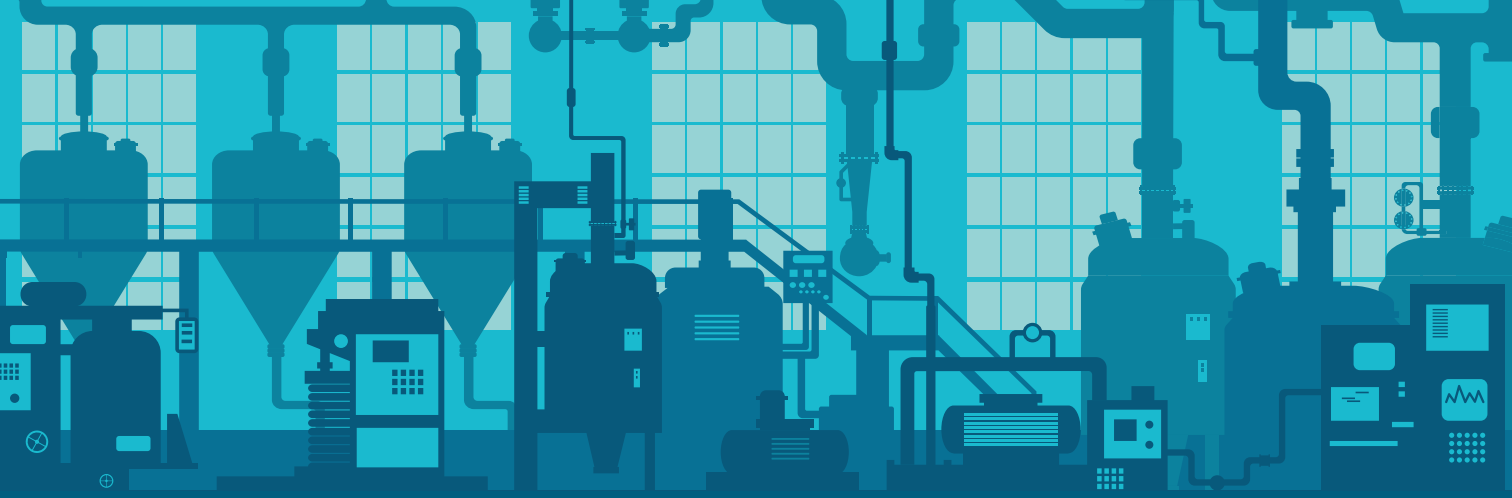

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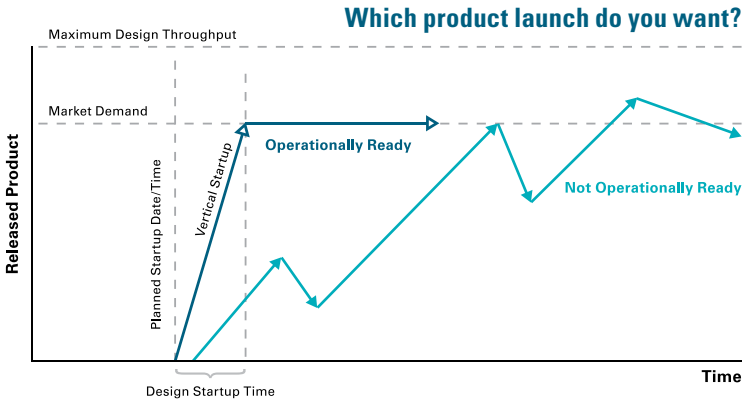

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