

# PHARMACEUTICAL ENGINEERING®

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# Continuous Manufacturing

**Removing Regulatory  
Hurdles for Continuous  
Pharmaceutical Manufacturing**

**ICH Q13 and What Is Next  
for Continuous Manufacturing**

**Agile, Data-Driven Life  
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## **14 REMOVING REGULATORY HURDLES FOR CONTINUOUS PHARMACEUTICAL MANUFACTURING**

Continuous manufacturing (CM) challenged regulators' expectations and regulatory frameworks. This article discusses how US regulators addressed the regulatory hurdles related to CM to broaden its adoption through engagement, regulatory science, guidance, and international harmonization.

## **20 ICH Q13 AND WHAT IS NEXT FOR CONTINUOUS MANUFACTURING**


The creation of a new ICH guidance document, Q13, presents an opportunity for industry and regulators around the world to connect and develop harmonized regulatory expectations for the continuous manufacturing of drug substances and drug products, resulting in an increased likelihood of implementation across the globe.

## **24 AGILE, DATA-DRIVEN LIFE CYCLE MANAGEMENT FOR CONTINUOUS MANUFACTURING**

Pharmaceutical continuous manufacturing (CM) is recognized as a key process intensification technology, with investment expected to rise in the coming years and the focus shifting toward biologics. This article provides a review on the current state of CM implementation, offers insights into life cycle management and regulatory aspects, and explains how a data and knowledge-centric approach to risk management can help CM achieve its full potential.

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**ON THE COVER** Medical glass vials moving forward on a pharmaceutical production line signify continuous manufacturing.



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## 36 A SYSTEMWIDE APPROACH TO MANAGING THE RISKS OF CONTINUOUS MANUFACTURING

Understanding and managing risks to continuous manufacturing (CM) technology is central to any decision to greenlight CM in a production-ready environment. Applying a systemwide risk management approach to manufacturing is essential to ensuring manufacturing projects are vetted in a comprehensive and consistent manner.

## 44 USP/BIOPHORM WORKSHOP ON CONTINUOUS MANUFACTURING BIOLOGICS

In the interest of understanding the current state of continuous manufacturing for biologics and to facilitate the path toward adoption of these promising technologies, the United States Pharmacopeia (USP) and BioPhorum jointly sponsored a hybrid workshop. This article summarizes trends from the workshop and ponders next steps.

### DEPARTMENTS

#### 6 MESSAGE FROM THE CHAIR

Board Elections and Our Strategic Plan

#### 10 WOMEN IN PHARMA® EDITORIAL

Can Communication in a Multigenerational Environment Be Inclusive?

#### 12 EMERGING LEADERS EDITORIAL

Continuity in Manufacturing and Industry Leadership

### PEOPLE + EVENTS

#### 52 Community of Practice Leader Profiles

52 Heather Watson, Chair of the GAMP® Global Steering Committee

53 Christian Wölbeling, Chair of ISPE's Pharma 4.0™ CoP

#### 54 A Comprehensive Reference for Continuous Manufacturing of OSD

#### 55 ISPE UK Emerging Leaders Awards

#### 56 Meet the ISPE Staff: Edyna Miguez

#### 72 Ad Index/Classifieds

### TECHNICAL

#### 58 AI AND LARGE LANGUAGE MODELS

##### ChatGPT, Bard, and Other Large Language Models Meet Regulated Pharma

ChatGPT and other large language models are positioned to change the world. They can also shift acceptance and prevalence of machine learning solutions in regulated industries in general. However, their arrival requires reconsiderations on risks, quality assurance, and validation from a 6xP perspective.

#### 66 ENERGY EFFICIENCY

##### Air Change Rate Reduction During Operation: Success at Roche/Genentech

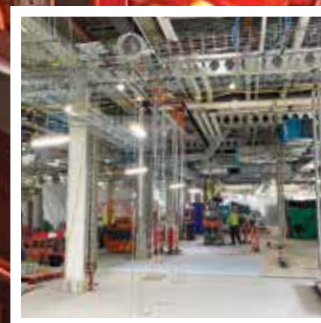
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Michael L. Rutherford

# Board Elections and Our Strategic Plan

It is starting to become more real that my term as Chair is winding down because the 2023–2024 International Board elections are happening.

We had our largest number of nominations yet this year, with an extremely strong group of potential Board candidates. Evaluating the candidates for the final ballot was a challenging process for the Nominations Committee.

I sincerely hope you, as the members of ISPE, took the time to cast your ballot and elect your International Board representatives. It amazes me every year that only 10%–15% of the membership votes. The independent service that manages the election process says this is very typical of organizations like ISPE, but I always wonder why.

I am curious if the significant increase in nominations will translate into increased members casting ballots this year. As a volunteer-based organization, member engagement is crucial to our success. The 2023–2024 International Board will be announced in September and will begin activities at our next major event on the ISPE International calendar, the Annual Meeting and Expo in Las Vegas, Nevada, 15–18 October. 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: CONTINUOUS MANUFACTURING

In 2017, Sau “Larry” Lee, PhD, Deputy Director of the Office of Testing and Research, and Chair of the Emerging Technology Team, Office of Pharmaceutical Quality, CDER, published a spotlight on CDER science entitled, “Modernizing the Way Drugs Are Made: A Transition to Continuous Manufacturing.” He discussed the differences between the traditional batch manufacturing methods, which involve multiple discrete steps and hold times, and continuous manufacturing, in which material is fed through an assembly line of fully integrated components to save time, reduce human error, improve quality, and allow for longer runs and more nimbleness, thereby reducing the likelihood of drug shortages. (Editor’s Note: Lee is co-author of the article on page 14.)

Dr. Lee emphasized that the transition to pharmaceutical continuous manufacturing was still in its early stages due to high startup costs, including the purchase of new technology and training staff, the revamping of industry infrastructure, and a serious commitment from a drug maker. But the economic analyses showed potential significant long-term savings. In addition, the technologies still needed to mature before being commercially viable, especially for certain types of drugs, such as biotech products. These biotech challenges were discussed in a PE article written by Robert Dream, PE, CPIP, PhD, Christoph Herwig, PhD, and Emilie Pelletier entitled “Continuous Manufacturing in Biotech Processes—Challenges for Implementation” in the November/December 2018 issue.

Jump ahead five years to 2023 and continuous manufacturing, especially in the solid dosage area, has moved forward, with numerous companies receiving product approvals from regulatory agencies. Regulatory agencies have kept pace with regulatory





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guidance to support these efforts as a result of great industry-regulatory collaboration. Numerous companies have been recognized in recent years for their innovation in continuous manufacturing with ISPE Facility of the Year Awards (FOYA) and the technology continues to expand to other areas of pharmaceutical manufacturing; hence, ISPE's focus this issue.


### STRATEGIC PLAN: ATTRACT NEW TALENT AND DEVELOP FUTURE LEADERS

As part of our 2023–2025 Strategic Plan to attract new talent, ISPE is passionately committed to investing—in partnership with the ISPE Foundation—in the future of the pharmaceutical industry through our student and Emerging Leaders programs. In March of this year, ISPE announced a unique opportunity for students and recent graduates to experience an ISPE conference in person.

For 2023, ISPE is providing grants for students and recent graduates to attend our two largest conferences: the 2023 ISPE Europe Annual Conference or the 2023 ISPE Annual Meeting & Expo. Thanks to this effort, more than 100 students and recent graduates will have the unique opportunity to experience an ISPE conference in person. Grant recipients receive in-person all-access registration to one of the conferences, a two-year ISPE membership, the option

to participate in the ISPE Emerging Leaders Hackathon, and travel reimbursement per the ISPE travel reimbursement policy (which covers airfare/train and hotel).

As a result of this program, 51 students and recent graduates attended ISPE's 2023 Europe Annual Conference in Amsterdam in May. The application window for attending ISPE's 2023 Annual Meeting & Expo in Las Vegas in October closes Thursday, 31 August 2023. More information and an application can be found at [ISPE.org/membership/student-recent-graduate-grant-program](https://ISPE.org/membership/student-recent-graduate-grant-program)

I encourage students and recent graduates to apply today for this unique opportunity. Grant recipients for the AM23 grant will be notified on Tuesday, 12 September 2023. I also want to encourage companies, vendors, affiliates, chapters, members, and company leadership to support this program in future years. These students and recent graduates represent our future, and you can help enable them to learn and see what the pharmaceutical industry is all about. 

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**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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Janette Buechler

# CAN COMMUNICATION IN A MULTIGENERATIONAL ENVIRONMENT BE INCLUSIVE?

The multigenerational environment we work in poses unique challenges that make effective communication skills as essential today as they have ever been.

Due to the complexity of a distributed and multigenerational workforce, myths and stereotypes have arisen around how different generations communicate. But these stereotypes are largely unfounded and can cause friction as we try to bridge the gap between different communication styles. In this article, I debunk some of the most common myths associated with how different generations communicate and collaborate in the workplace.

## MYTH 1: MILLENNIALS ONLY COMMUNICATE USING TECHNOLOGY

One of the most common myths about millennials is that they only communicate through technology. While it is true that millennials have grown up in a world where technology is a mainstay of communication, they often participate in face-to-face interactions. A report in the Denver Business Journal found that millennials prefer face-to-face communication when collaborating with colleagues [1].

## MYTH 2: BABY BOOMERS DON'T WANT TO LEARN NEW SKILLS

Another common myth is that baby boomers prefer to stick to long-established methods of communication. Although there may be a comfort level with familiar tools and techniques, they still value education. According to an AARP survey, 74% of older workers said the opportunity to learn something new is critical to their view of the ideal job. An article in Forbes noted that employee training programs tend to ignore experienced workers despite their desire to learn [2]. Which raises the question: Are employers missing an opportunity?

## MYTH 3: GENERATION X ARE THE FORGOTTEN GENERATION

Pew Research calls Generation X the forgotten generation [3]. Why? Perhaps because they are a small group between the larger baby boomer and millennial generations. However, this does not mean they are less important in the workplace or less capable of effective communication and collaboration. They are also referred to as the “most connected” generation, bridging the gap between the generations older and younger than them. Gen Xers can

understand both long-established and modern communication methods and are fluent in both.

## MYTH 4: GENERATION Z AVOIDS FACE-TO-FACE INTERACTION

Generation Z, the youngest generation in the workplace, is often stereotyped as being glued to their smartphones and only communicating through social media. Although it is true that Generation Z is consumed with handheld technology, they thrive on human interaction while keeping up with their friends and family online. According to a LinkedIn Learning survey, while Generation Z enjoys using technology to communicate, it's not their preferred method of communication in the workplace [4]. They also value face-to-face interactions.

## MYTH 5: DIFFERENT GENERATIONS CAN'T WORK TOGETHER WELL

Perhaps the most harmful myth is that different generations cannot work together effectively due to their varied communication and styles. While each generation may have its own preferences, effective communication is ultimately about respecting each other's strengths and weaknesses. Findings suggest the differences between these groups are actually quite small. Perhaps it's not the differences between generations but the belief that they exist that influences our communication. Coming to terms with the value of different generational perspectives leads to better decision-making overall and potentially better collaboration. 🌟

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## About the author

**Janette Buechler** is the Executive Director of sales and marketing for Pharmatech Associates. She has been involved in Women in Pharma® since joining ISPE. Her volunteer work as a member of the Women in Pharma International Steering Committee seeks to expand the program to other geographical regions and is inspired by the increased involvement and progress toward its mission. She has been an ISPE member since 2012.

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# CONTINUITY IN MANUFACTURING AND INDUSTRY LEADERSHIP

The pharmaceutical industry is highly regulated, with strict standards for the production and distribution of medications. However, the concept of continuous manufacturing (CM) has revolutionized the way pharmaceutical products are made.

Continuous Manufacturing speeds up the development process, reduces errors through monitoring quality parameters, and lowers the costs of manufacturing. Similarly, continuity and collaboration are vital in developing leaders, achieving growth, and impacting future community members.

## IMPORTANCE OF CONTINUITY IN DEVELOPING EMERGING LEADERS

As a member of ISPE's Emerging Leader (EL) community, I have seen firsthand the impact of continuity and collaboration in developing the next generation of pharmaceutical industry leaders. To develop and advance as leaders, we engage with local affiliates, facilitate thought leadership events, and collaborate nationally and internationally. This shift has occurred gradually, similar to the move from batch production to CM.

## ROLE OF COLLABORATION IN ACHIEVING SUSTAINABLE GROWTH

Sustainable growth requires continuity, and the ISPE ELs ensure continuity through their involvement in European and international conferences, as well as local events. ELs have moved from being guests to contributors to program committee members, moderators, and co-chairs of educational tracks. Hackathons, launched in 2017, have become must-attend events for students seeking to work in the pharmaceutical industry. More than 100 students attend each year to solve real-world industry challenges with experienced coaches from the industry.

## BENEFITS OF ATTENDING CONFERENCES AND INVESTING IN EMERGING LEADERS


ISPE has launched 100 travel grants to the ISPE European Annual Conference in Amsterdam and the ISPE Annual Meeting in Las Vegas. This sponsorship program makes collaboration, education,

and networking even more accessible for young leaders working in pharmaceutical engineering and students seeking to join the pharmaceutical industry. Committed to helping professionals expand their network, experience, and knowledge within the pharmaceutical industry, ISPE provides the resources to make that possible. Emphasis on continuity helps bridge gaps across countries and speeds up innovation and progress.

## IMPORTANCE OF RESILIENCE

Continuity is not possible without resilience. Boosting resilience requires rest and breaks to come back to professional settings with energy and passion. Leaders who are overextended and in survival mode lack the mental capacity for innovation or progress. Like production lines that need proper maintenance, bringing yourself to be the best version of yourself requires clear minds, rested bodies, and proper fuel. As emerging leaders, we reiterate the importance of balance on a small, local level, and a large, international level.

The biggest benefit of becoming an ISPE member and joining forces with the ELs is the continuity that comes from it. It takes an investment from all of us, but we are stronger together. Participation in conferences, events, and case studies can boost entire organizations and industries because talented leaders come together to overcome obstacles. Our industry is only as powerful as all of us. To have a lasting impact, we must remain committed to continuity and collaboration.

In conclusion, continuity in manufacturing has changed the pharmaceutical industry, and now it is changing industry leadership. Continuity and collaboration are crucial in developing emerging leaders, achieving sustainable growth, and impacting future community members. Boosting resilience among young leaders is vital in promoting innovation and progress. The investment in continuity and collaboration will have a lasting impact on the pharmaceutical industry and its leaders. 

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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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# REMOVING REGULATORY HURDLES for Continuous Pharmaceutical Manufacturing

By Adam C. Fisher, PhD, Thomas O'Connor, PhD, Joel Welch, PhD, and Sau (Larry) Lee, PhD

Continuous manufacturing (CM) challenged regulators' expectations and regulatory frameworks. This article discusses how US regulators addressed the regulatory hurdles related to CM to broaden its adoption through engagement, regulatory science, guidance, and international harmonization.

Continuous reactions and processes are a fundamental concept taught to all undergraduate chemical engineers, often in their junior year. The concept teaches students about reaction kinetics and process dynamics and for many it draws the first clear link between the molecular principles of chemistry and the mathematical principles of calculus. Most chemical engineering curricula also include a capstone design course in which soon-to-be-graduates tackle process design problems that approximate the challenges they might encounter in the workforce.

For many years, undergraduate students have tackled the design, development, and financial justification of continuous chemical processes that are found in the commodity chemicals, food and beverage, and petrochemical manufacturing industries. Generally, CM is fit for processes with high repeatability requirements, as is the case for pharmaceuticals [1].

Burgeoning chemical engineers joining the pharmaceutical manufacturing workforce are often surprised to discover that few manufacturers have adopted CM for either drug substance (reaction chemistry) or drug product (formulation). As these engineers understand, CM may not be fit for every drug substance or drug product manufacturing process, but it can bring potential advantages in many cases, most notably better efficiency, reduced costs, and improved process control. For example, one pharmaceutical

company that switched to CM reported a 50% reduction in operating costs, a 33% reduction in waste, an 80% reduction in manufacturing and testing cycle time, and a 66% reduction in time from testing to release [2, 3].

Key differences between CM of pharmaceuticals versus other chemicals relate primarily to volume and runtime. For some commodity chemicals, CM over very long runtimes is possible and financially feasible. For pharmaceuticals, however, the continuous production volume, and hence runtime, is flexible to meet variable market demand. For example, a runtime can be short when the drug is used by a small patient population. Some continuous pharmaceutical processes are designed to reduce the runtime associated with a batch process. This high-value/low-volume proposition leads process designers to consider a continuous process based heavily on their desire for a high level of process control. In the past, commercial process equipment for CM was only available at large volume production levels, beyond the scale desired by many pharmaceutical manufacturers [4].

Over the past two decades, process equipment has become available at scales more adaptable to continuous pharmaceutical production [5]. In addition, there are human elements to consider. For example, one pharmaceutical company reported adopting continuous technology when faced with the challenge of designing a commercial Grignard reaction and accounting for its associated spontaneous heat release [6]. In this case, there was a benefit to using a safe and controlled continuous process with minimal operator involvement and less manual material movement between unit operations.

## REGULATORY SUPPORT AND PERFORMANCE

As pharmaceutical process designers began recognizing the benefits of CM in the mid-2010s, FDA's Center for Drug Evaluation and Research (CDER) began engaging with prospective manufacturers



to discuss, identify, and resolve potential technical and regulatory issues regarding the development and implementation of CM prior to filing regulatory submissions. In 2014, CDER established the Emerging Technology Program (ETP) within its Office of Pharmaceutical Quality to better facilitate the adoption of emerging technologies such as CM [7].

A critical feature of the ETP is representation from all relevant FDA quality assessment and inspection programs, from early engagement with stakeholders through application submission and assessment. Early interactions can focus on the technology and its application and do not need to be specific to a product or regulatory submission. Owing to the engagements through the ETP and the addition of key personnel with experience in CM in the petrochemical industry, CDER approved the first regulatory submission incorporating CM for a small molecule drug product in 2015.

The following year, CDER approved the first switch from batch manufacturing to CM for a drug product. Since then, more pharmaceutical manufacturers have started to both develop and implement CM for commercial production. The ETP has now accepted 50 proposals related to CM and CDER has approved a number of diverse submissions, including:

- A drug product employing CM for active pharmaceutical ingredient synthesis
- A continuous biomanufacturing process
- A drug product that can be made using a batch or continuous process
- Three drug products that can be made using the same CM line

With the benefit of hindsight, 2014 may have been the tipping point for CM adoption for pharmaceuticals. In addition to forming the ETP, CDER participated in the first International Symposium on Continuous Manufacturing of Pharmaceuticals, sponsored by the Novartis-MIT Center for Continuous Manufacturing, to discuss the opportunities, technologies, and regulation of CM.

This meeting resulted in eight seminal white papers that defined some of the initial challenges and benefits for the pharmaceutical industry in adopting CM related to regulatory considerations [8], CM for finished dosage forms [4], continuous bioprocessing [9], equipment and analytical companies [10], control systems engineering [11], CM for drug substances [12], future supply chains [1], and the development and manufacturing structure [13]. An FDA-authored paper indicating support for the implementation of CM using science- and risk-based approaches followed soon thereafter [14]. The fourth such symposium was recently held in April 2023, in part to celebrate the CM implementation successes that have occurred since the first meeting in 2014.

It is instructive to revisit the regulatory concerns shared in those early papers. These included, for example, defining a batch, establishing representative sampling, handling deviations, forming testing rationale, setting raw material specifications, identifying sources of variability, and enabling manufacturing changes. Two of the most significant policy developments since 2014 have been the release of the *Quality Considerations for Continuous*

*Manufacturing* draft guidance in 2019 and the International Council for Harmonisation (ICH) Q13 guidance on CM of drug substances and drug products in 2023 [15].

The guidance covers the regulatory considerations identified in 2014, including the definition of a batch (which can be defined in terms of quantity of output or input material or runtime at a defined mass flow rate), process dynamics (including sampling and diversion strategies), changes in production output (including increasing run time or flow rate, scale-up, or scale-out), and continuous process verification. In addition to the FDA, health authorities in Canada, Europe, Australia, Japan, Switzerland, and New Zealand have also approved applications with CM for the production of solid oral dosage forms [16].

Now some manufacturers are moving beyond CM of drug substance or drug product and are instead developing CM of drug substance and drug product. End-to-end continuous processes flow from starting materials to finished dosage forms. CDER funded the National Academies of Sciences, Engineering, and Medicine (NASEM) to host a series of workshops that resulted in a consensus study report “Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, Recommendations” [17].

In this report, NASEM foretold manufacturing processes that integrate all processing steps from synthesis of an active pharmaceutical ingredient to final drug product. Such end-to-end continuous processes bring different regulatory considerations; for example, sequential continuous unit operations eliminate the accumulation of process intermediates and perhaps even isolated drug substance.

Because much of the existing regulatory framework is built around the manufacture of a discrete drug substance and the separate manufacture of drug product using isolated drug substance, end-to-end CM challenges the regulatory expectations of the existing framework. To clarify regulatory expectations for end-to-end CM, ICH Q13 devoted an annex to describing the unique scientific and regulatory considerations of an end-to-end CM process for solid oral drug products. In addition, there are related technologies that might play a role in this new manufacturing paradigm, such as artificial intelligence, machine learning, and distributed manufacturing. These technologies might even combine to result in end-to-end, distributed strategies comprising CM units using artificial intelligence to enable adaptive process and product quality controls.

To address the regulatory framework for these additional technologies, CDER began an initiative called the Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) to prepare a regulatory framework to support the adoption of prioritized advanced manufacturing technologies that could bring benefits to patients [18]. In 2022, CDER released a discussion paper for stakeholder feedback on distributed and point-of-care manufacturing and in 2023 released a discussion paper on artificial intelligence in pharmaceutical manufacturing [19, 20]. The purpose of these discussion papers is to capture early stakeholder

CM may not be fit for every drug substance or drug product manufacturing process, but it can bring potential advantages in many cases, most notably better efficiency, reduced costs, and improved process control.

feedback to proactively prepare the regulatory framework for the implementation of critical advanced pharmaceutical manufacturing technologies.

## REGULATORY SCIENCE AND RESEARCH PERFORMANCE

Knowledge and training enable the regulatory ability and readiness to evaluate CM technology. CDER's science and research program has fueled over 60 intramural and extramural research projects to build a knowledge base for advanced manufacturing technologies, including CM. CDER-funded research on CM has included work on process development, advanced control strategies, modeling approaches, and Industry 4.0 [21]. Because CM can apply to diverse product types, research includes CM of active pharmaceutical ingredients, biotechnology drug products, and small molecule drug products [22, 14].

Researchers have covered continuous chemistry approaches such as continuous crystallization [23, 24] and flow chemistry [25, 26], as well as a material library [27] related to drug product manufacturing. Biotechnology research has covered continuous biomanufacturing issues such as viral clearance [28, 29], cell separation [30], and in-line process monitoring [31]. Research is preparing for CM of increasingly diverse drug product types in the future such as extended-release tablets [32, 33], liposomal formulations [34], and polymeric micelles [35].

Significant progress has already been made in the development and implementation of integrated process models related to blending [36], flowsheet simulation [37, 38], managing abnormal conditions [39], and twin-screw wet granulation [40]. Process models are useful tools to estimate the impact of potential variations of model inputs (e.g., the process and equipment conditions, raw materials, and environmental factors) on model outputs (e.g., product quality attributes). The results produced from intramural and extramural research projects are fundamental to the performance and impact of CDER's advanced manufacturing initiatives.

Though advanced manufacturing technologies are employed in less than 1% of human drug applications to the FDA, more than 10% of CDER's active research project portfolio addresses some element of advanced manufacturing. The FDA uses the results of these research projects to develop regulatory recommendations for the industry to guide product and technology development; knowledge to inform new standards, guidances, and policies; and materials for training FDA staff.

Specifically, outcomes of CDER-funded research were used to develop recommendations to guide product and technology development under the ETP, evaluate regulatory submissions that included CM, and inform the ICH Q13 guidance and the developing ICH Q5A guideline revision, *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*.

Process models developed through CDER research have been applied to aid the assessment of CM processes in regulatory submissions. CDER researchers who developed these models were recently awarded the American Institute of Chemical Engineers Pharmaceutical Discovery, Development, and Manufacturing Forum Award for Excellence in Integrated Quality by Design Practice. The national award recognized their contributions in advancing the use of modeling and simulation for quality risk management of CM processes [41]. Models can be used to visualize differences between manufacturing processes and control strategies, a powerful tool for training FDA staff and implementing modeling and simulation in the industry. The knowledge gained from CDER-funded research on CM drives toward the goal of better design and control of manufacturing processes in pharmaceutical supply chains.

## REMOVING REGULATORY HURDLES

Although there are financial and logistical challenges to adopting CM, some myths persist. It has been clear that CDER supports the adoption of CM, but some have opined that C-suite leaders continue to resist CM acceptance [42]. Still others are concerned that the FDA is mandating the use of CM. The FDA approves drugs if they comply with applicable standards, regulations, and laws. There is no regulatory requirement to use CM. While there can be public health benefits to CM, such as increased reliability of supply, these benefits may be realized for some but not all drug products. Critics are quick to note that CM has thus far been approved for innovator drug products but no generic products.

However, CM is not just for innovator companies; multiple developers of generic drugs have engaged with CDER's ETP on the use of advanced manufacturing technologies for generic drug products. Another concern of generic drug companies is that they might be required to implement CM if an innovator company has done so. There is no regulatory basis to this claim. If an innovator company implements CM, the standards for generic drug application assessment and approval would not change. Specification criteria are established based on relevance to the patient and not on process capability. Additionally, some are hesitant to use CM

**Table 1: Regulatory hurdles and FDA actions.**

Regulatory Hurdles for CM	FDA Actions
Manufacturers were hesitant to adopt CM without additional engagement from the FDA.	In 2014, CDER created the ETP to support stakeholders in developing and implementing CM.
Manufacturers were hesitant to adopt CM before the FDA approved a product manufactured with CM.	In 2015, CDER approved the first product manufactured with CM, and has since accepted 50 proposals from industry into the ETP and approved 13 more submissions.
Manufacturers were hesitant to adopt CM for existing products before the FDA approved a switch from batch manufacturing to CM.	In 2016, CDER approved the first switch from batch to CM for a drug product.
Manufacturers were hesitant to adopt CM without guidance from the FDA.	In 2019, FDA released the draft guidance <i>Quality Considerations for Continuous Manufacturing</i> .  In 2022, FDA published the draft revision to the guidance <i>Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin</i> , which includes considerations for viral safety evaluation for CM.
Manufacturers were hesitant to adopt CM because they feared the timelines for FDA approval might be longer.	In 2022, CDER released data showing that applications using CM were approved faster than similar applications using batch manufacturing.
Manufacturers were hesitant to adopt CM without internationally harmonized guidance.	In 2023, the FDA released final internationally harmonized guidance <i>Q13 Continuous Manufacturing of Drug Substances and Drug Products</i> .

because they are afraid it will take the FDA longer to review and approve their application [17].

Although there is no prescribed review timeline for CM applications, other than those related to user fee goal dates, CDER conducted a self-audit of the CM regulatory submissions and outcomes in the US [43]. There is an unfortunate prevailing assumption among manufacturers that applications with new technologies take the FDA longer to approve, but this audit found the opposite.

Through early engagement with CDER under ETP, CM applicants had shorter times to approval and marketing compared to batch applicants: three months faster to approval and four months faster to marketing. This faster approval translated to several hundred million dollars in early revenue for these manufacturers.

This audit also found no substantial regulatory barriers associated with common regulatory interactions related to implementation of CM and faster scale-up as compared to batch manufacturing. The result was earlier patient access to medicines and a potential \$100–\$500 million US in early revenue benefit for manufacturers. Over time, major regulatory hurdles for CM have been cleared (see Table 1).

Some key findings of the financial benefits of CM are worth emphasizing here. In a study of the comparative investment analysis of batch versus continuous pharmaceutical manufacturing, the lower costs associated with CM are expected to lead to brand and generic companies investing in CM [44]. Further, CM makes manufacturing solid oral dosage form pharmaceuticals more economically attractive in the US than foreign manufacturing, and investing in CM in the US under current tax rates results in positive value over batch manufacturing in China or India for brand and generic companies.

This analysis suggests that CM of solid oral dose pharmaceuticals in the US has the potential to be more economically attractive than foreign manufacturing. Indeed, it seems CM has


already been an effective strategy in promoting domestic manufacturing, as 8 of the 13 drug products made using CM are produced in facilities in the US. The development of and funding for CM for human drugs and biologics has exploded in the COVID-19 era [45]. Federal funding supported the development of domestic CM facilities for drug substances and drug products, and some of these facilities are now approaching commercial readiness.

## CONCLUSION

In the future, CM, like any technology, cannot remain in an emerging status forever. An important feature of the ETP is the graduation of a technology such that an application’s assessment can be handled by standard, trained CDER review staff. As the ETP passed the landmark occasion of the 150th FDA-sponsored emerging technology meeting, it reached another significant milestone with the first technology to graduate from the ETP: continuous direct compression (CDC).

CDC is a pharmaceutical manufacturing process that consists of dispensing, mixing, and compressing using equipment that is integrated, resulting in no breaks in the process. CDC can improve the assurance of product quality by minimizing human intervention and taking advantage of process analytical technology. Graduation means that industry developed the sufficient regulatory submissions related to the technology and CDER expanded its capability through comprehensive training of its quality assessors on CDC technology, such that any application assessment team can fully handle such a technology when referenced in a submission, independent of the ETP. Due to the expanding workload of the ETP, CDER has begun implementing ETP program enhancements to improve strategy and operation and to enhance communication with those adopting new technologies. Eventually all CM technologies will graduate from the ETP.

New legislation also brings new changes and opportunities for the regulation of advanced manufacturing technologies, such as CM. For example, the reauthorized user fee program of the Prescription Drug User Fee Act (PDUFA VII) aims to advance the implementation of innovative manufacturing technologies. To this end, the FDA will conduct a workshop that includes industry and public feedback and publish a draft strategy document for public comment on innovative manufacturing technologies. This document will outline the strategy to facilitate the implementation of innovative manufacturing technologies, including addressing barriers to their adoption.

These engagement opportunities will help the FDA further encourage submissions for products made using innovative manufacturing technologies that ensure product quality and a robust manufacturing process. The Consolidated Appropriations Act 2023 under the Food and Drug Omnibus Reform Act of 2022 (FDORA) pushes this concept further. For example, many of its provisions relate to advanced manufacturing, including issuing guidance, holding a public meeting related to the designation of advanced manufacturing technologies, and establishing the ETP in statute. As long as new manufacturing technologies are developed, there will be opportunities to implement innovations in pharmaceutical manufacturing, and concomitant needs for regulatory support. 

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# ICH Q13 AND WHAT IS NEXT for Continuous Manufacturing

By Gabriella Dahlgren, PhD, and Douglas B. Hausner, PhD

The creation of a new ICH guidance document, Q13 [1], presents an opportunity for industry and regulators around the world to connect and develop harmonized regulatory expectations for the continuous manufacturing (CM) of drug substances and drug products, resulting in an increased likelihood of implementation across the globe.

ICH Q13 defines CM as follows: “CM involves the continuous feeding of input materials into, the transformation of in-process materials within, and the concomitant removal of output materials from a manufacturing process” [1]. Although CM technology has been around for decades, it does present some novel challenges to the pharmaceutical industry, especially when the goal is to supply therapeutics globally. This has stemmed from a lack of familiarity with the “new to pharma” technology among global regulatory bodies, or at least the perception thereof.

## MEETING A NEW NEED

Globally, there is an increased demand for new therapeutics and pressure to deliver them at a lower cost. And, as the COVID-19 pandemic has shown, being able to rapidly scale up and scale out the manufacturing process is a challenge for the pharmaceutical industry. CM has the potential to address several of these requests. Increased implementation can also help realize the other benefits inherent to CM, such as:

- Additional manufacturing options, which offer increased flexibility and faster to market development compared to traditional options, to address public health demands such as drug shortages and unmet medical needs
- More advanced controls to assure product quality, including improved robustness and manufacturing process capability

- Reduced environmental impact such as material consumption, waste generation, and reduced equipment and facility footprint

However, general guidance on CM will not address all the unmet needs for regulators and industry across different modalities and geographical regions. This article highlights the overall benefits and scope of Q13, as well as what we see as the next set of opportunities to further expand the adoption of CM across the globe.

## Q13 DEVELOPMENT TIMELINE

The process of drafting the new guidance document was initiated in earnest in November 2018 when the concept paper [2] and business plan were endorsed. Over the next two and half years, the Expert Working Group (EWG), in collaboration with extended subteams from regulatory bodies and industry groups, crafted the guidance and had a draft ready for public commenting in July 2021.

Q13 generated significant interest. Over the next year, the EWG reviewed it and focused on reaching consensus around critical comments. An updated draft was reviewed by the EWG members and their organizations in October 2022. The timeline continued to follow what was originally proposed in the business plan: sign off (step 3) and then adoption (step 4) in November 2022. Since then, agencies have begun officially adopting the guidance, with the FDA doing so in March 2023. The European Medicines Agency (EMA) published an effective date of July 2023 and an Implementation Working Group (IWG) has been formed to develop accompanying training material.

## Q13 SCOPE

The intent of Q13 is to build on existing ICH quality guidelines while providing clarification on CM concepts. This includes describing the scientific approaches that are unique to this manufacturing process methodology and presenting regulatory considerations that are specific to CM of drug substances and drug products, with a focus on an integrated system versus an

individual continuous unit operation (which has already been employed in the pharmaceutical industry for decades).

The goal is to address the full life cycle of the manufacturing process, including development, implementation, commercial operations, and life cycle management. A key thrust of the guidance is to highlight when concepts that are unique to CM need to be part of the regulatory filing versus appropriately captured within each companies' pharmaceutical quality system (PQS).

Overall, Q13 is focused on the "what" not the "how," which is what manufacturers want to see to allow for product-, modality-, and company-specific approaches to be taken. However, this format can delay implementation within some companies because there is less prescriptive information on exactly how to do, or why not to do, something. Q13 seeks to enable CM while not being prescriptive and allowing for future innovation through the use of annexes that provide additional detail as far as how the specific concepts relate to small molecule drug substance, solid dose drug product, large molecule (proteins), and integrated end-to-end manufacturing processes.

Future updates to these annexes, in concert with training materials and similar public domain contributions from ISPE and others, are intended to aid adopters in defining their pathway. Because the use of CM is expected to continue to grow beyond the current most common implementation for small molecule drug product, the focus on the guidance has been on general concepts that can be applied to any technology, dosage form, or molecule type. However, this has the caveat that because small molecule drug product is the most mature CM platform, the guidance text may lean toward language and definitions for this modality; thus, some of the text may not apply to all modalities and platforms.

Due to the novelty of CM in our industry and the focus on the "what" in the guidance, it does require that each company clearly articulates how a specific approach addresses a required "what." This is where the planned training material will become a critical aid, as it can and will highlight various approaches to meet a specific need (building on the guidance and especially the annexes). It should be noted that the guidance is focused on topics that are unique to CM, but not necessarily complementary or enabling technologies unless they are unique to CM.

Some items that are therefore out of scope of this guidance (beyond being mentioned as tools that can accompany CM) are process analytical technology (PAT), modeling, and in-depth discussion around continuous process verification. Many in the industry feel it's critical to achieve global regulatory harmonization in some of these areas in the near future for full deployment and implementation of CM. Some of these potential bottlenecks are discussed in detail next.

## Q13 TRAINING MATERIALS

Although the guidance document has been completed and was endorsed in January 2023, the work is not yet done. The EWG has now transformed to an IWG focused on developing training material throughout 2023 to complete the guidance in June 2024. The

intent is for the training material to address the different levels of understanding of key scientific and regulatory concepts among regulators and industry stakeholders.

Presentations, video, industry-led training, regulatory-only training, and in-person training at CM facilities or labs (when possible) enable detailed dissemination and discussion of CM concepts and provide an opportunity to include practical examples to illustrate how Q13 can be applied in development, routine operation, and life cycle management of CM processes as well as potential examples of how complementary technology such as PAT and modeling is practically applied to CM.

## FUTURE ANNEXES AND TRAINING

Although Q13 goes a long way toward aligning global regulatory bodies and enabling the adoption of CM, there are still elements of implementation that would benefit from further support. Overall, while guidance helps with clarity on how to proceed for those who have chosen to move forward with a specific technology, there are aspects related to making the business case that remain unaddressed.

Whether using traditional batch manufacturing or CM, the final product delivered to the customer remains the same. Therefore if the bar is higher for the new technology, transition to it will remain slow, even when there are benefits to transitioning. Enabling adoption of technology is one of the driving forces for harmonization and ICH Q13.

As CM has been adopted in recent years, initially for solid dose processes, we have seen expansion and evolution of the equipment offerings to the point that we have a variety of options. Although a number of different manufacturing options exist, including different forms of wet granulation akin to traditional batch manufacturing, adoption and signals on future utilization have been primarily for direct compression processes. At the same time, as first adopters grow the number of products within their CM portfolio, network strategy decisions come into play.

Within Q13 there is very little guidance on process transfer and equivalency for CM processes. The guideline does address scale-up, but primarily from the standpoint of utilization within the same process train, or a "like-for-like." It doesn't really address process or equipment changes other than to say "it may be possible." This creates a situation where technology users will either a) copy and paste the same equipment, controls strategies, PAT, etc., which limits the use of new and improved options; b) link a process to a single process train, limiting supply chain flexibility and creating risk; or c) adopt a costly strategy of what is essentially a new process development activity to move products within or in/out of network.

When considering the same situation for traditional batch manufacturing, there are guidelines like scale-up and post-approval changes (SUPAC) guidance that aid in identifying levels of change and associated chemistry, manufacturing, and controls (CMC) changes; testing; and reporting. Given the similarity in design and operating principles of continuous direct compression manufacturing trains and processes, it would

benefit the adoption if the requirements for changing equipment or manufacturing site were outlined. While the extent to which this has been an obstacle presented to regulatory bodies may be small, the perception without guidance has led to an apprehension among early adopters.

With regard to network strategy, many early adopters have sought to minimize differences and to invoke a “like-for-like” strategy as outlined within the scale-up portion of ICH Q13. As already mentioned, this type of strategy limits the opportunities to make changes based on lessons learned or improvements available in the market. Additionally, it makes it more difficult to outsource manufacturing to a contract manufacturer because the like-for-like equipment may not be available even if there’s capacity on another highly similar process train.

This then makes it a more challenging situation for contract development and manufacturing organizations (CDMOs) to aid in expanding adoption (and address commercial demand), as it is not financially viable to have the like-for-like process train of multiple customers, particularly when competing against traditional batch manufacturing on price. Although there has been a push for modularity within CM systems in recent years that has been mostly embraced by equipment manufacturers, which would make it easier to modify systems to be more similar, additional guidance on equivalency would help provide clarity and ease the perception of the need for like-for-like systems.

Over the past decade or more, as CM has entered the market, there have simultaneously been significant advances in modeling techniques that can be used to develop and support product and process development. While there has been strong support for these advances from many of the leading regulatory authorities, the level to which this is addressed within ICH Q13 is quite minimal. Q13 essentially redirects to ICH Q8/Q9/Q10 implementation for regulatory expectations on process models [3], which was released more than a decade prior to Q13.


Although the ICH Q8/Q9/Q10 Implementation guide does a good job of defining the categorization of models and the corresponding requirements for their development, implementation, and reporting, some level of detail or example on what is the same and different when considering CM would be beneficial in aiding adoption. Q13 has a set of annexes that help relate the guidance elements more specifically to various implementations of CM for drug substance and drug product processes for small and large molecule. Still, there is not a great deal of emphasis on the modeling aspects within these annexes aside from residence time distributions (RTDs).

Process modeling of a process maintained under a state of control nearing steady-state operation allows for further utilization of modeling tools and models that bridge between development and process control. There have also been a number of advances in process modeling as well as PAT and real-time release modeling that could be further highlighted through a Q13 lens. There are plans to update the Q13 annexes in the future and additional emphasis on this topic with linkages to other updated or new guidance documents should be included at that time.

## CONCLUSION

Over the course of the last decade, and even more so since the approval of the first product made by CM in 2015, there has been a significant amount of talk within the industry about the transition to the new technology. This paradigm shift has been slower than many expected at that time, with the main drivers being clarity on global regulatory expectation coupled with the fact that it didn’t enable a new class of therapies, only the manufacturing processes for existing ones.

ICH Q13 goes beyond what individual regulatory bodies (such as the FDA and the Pharmaceuticals and Medical Devices Agency [PMDA] who first published draft guidance documents) can do, by pulling the global regulatory and industrial community together to align or harmonize on the key aspects necessary for utilization of CM technology. While the work to transition the industry to this modern mode of manufacturing is not complete, ICH Q13 is a crucial step in the right direction. Especially because this will reach across the globe aiding in understanding of CM from health authorities that are less familiar with the topic to date.

The guidance will also make it feasible for smaller pharmaceutical companies that may have less internal expertise to employ this new manufacturing approach. The next phase of collaboratively developing training material to expand on the key topics in Q13 as well as complementary technology will further expand the deployment of CM as technology catches up for new modalities. 

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# AGILE, DATA-DRIVEN LIFE CYCLE MANAGEMENT for Continuous Manufacturing

By Rui César Silva, PhD, Rui Almeida, Pedro Ferreira, José C. Menezes, PhD, and Ângela Martinho, MEng

Pharmaceutical continuous manufacturing (CM) is recognized as a key process intensification technology, with investment expected to rise in the coming years and the focus shifting toward biologics. This article provides a review on the current state of CM implementation, offers insights into life cycle management and regulatory aspects, and explains how a data- and knowledge-centric approach to risk management can help CM achieve its full potential.

In recent years, global pharmaceutical supply chains, still based on traditional batch- and intermediates-based manufacturing, were overwhelmed by their own vulnerabilities and inefficiencies, and were stressed to the brink of failure as a result of the SARS-COV-2 pandemic. Acknowledging this concern, regulatory agencies have been devising strategies to prepare for future global events.

One approach was to enforce their support for advanced manufacturing approaches such as process intensification by creating working groups such as the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research's (CDER) Emerging Technology and Centre for Biologics Evaluation and Research's (CBER) Advanced Technologies programs, the European Medicines Agency's (EMA) Process Analytical Technology (PAT) team, and the Pharmaceuticals and Medical Devices Agency's (PMDA) Innovative Manufacturing Technology working group [1].

CM is a method of manufacturing products and processing materials without disruption and with constant material feed and removal. It is recognized as a key process intensification approach.

Although it has been widely adopted in other industries, the pharmaceutical industry has yet to do so, and most drug production still relies on the longstanding batch manufacturing process [2]. CM can integrate with the PAT and quality by design (QbD) approaches of manufacturing that are capable of increasing the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing [3]. As the pharmaceutical industry shifts its focus to biologics, the investment in CM elements in industry is expected to increase considerably. This is demonstrated by the rise from \$1.05 billion US in 2021 to \$1.9 billion US in 2022 for the global market share for prescription drugs produced using CM [4, 4].

## A RETROSPECTIVE JOURNEY

In 2015, Vertex's Orkambi was the first approved drug produced under a CM process for the treatment of cystic fibrosis. Vertex continued to invest in CM with two additional approved drugs—Symdeco/Symkevi in 2018 and Trikafta in 2019—with the same indication. As of 2022, there were 15 drugs (see Table 1) manufactured using CM elements that have received FDA approval, with GSK, Pfizer, and Vertex owning approximately 60% of the market share, followed by Janssen/J&J with about 13%. Several of these drugs, such as Pfizer's oncology drug Daurismo (glasdegib), were initially approved with a batch production process and then transitioned to CM afterward. AstraZeneca's Imjudo has some of the isolation steps accomplished continuously [3, 5, 6].

Historically, the highest number of FDA approvals—60% of total marketed CM drugs—occurred from 2018 to 2020 (see Table 1) and although 2021 approvals decreased to pre-2018 levels, 2022 saw two approvals: 13% of total marketed CM drugs. An average of two approved drugs via CM per year since 2015 shows that progress has been slow but steady and that interest in CM and its potential has been sustained. An integrated end-to-end continuous drug substance to drug product process is yet to be implemented or approved.

**Table 1:** List of FDA-approved commercial products using CM elements [6].

Product	Nonproprietary Name	Indication	Company	Approval Year
Orkambi	Lumacaftor, ivacaftor	Cystic fibrosis	Vertex	2015
Prezista <sup>1</sup>	Darunavir	HIV	Janssen (J&J)	2016
Verzenio	Abemaciclib	Breast cancer	Eli Lilly	2017
Symdeko/Symkevi	Tezacaftor, ivacaftor	Cystic fibrosis	Vertex	2018
Daurismo	Glasdegib	Myeloid leukemia	Pfizer	2018
Tramacet	Tramadol, paracetamol	Pain	Janssen (J&J)	2018
Trikafta	Elexacaftor, ivacaftor, tezacaftor	Cystic fibrosis	Vertex	2019
Dolutegravir	Doluegravir	HIV	GSK	2019
Fluticasone	Fluticasone ropionate	Allergy relief	GSK	2019
Duvroq	Daprodustat	Renal anemia	GSK	2020
Xofluzza	Baloxavir marboxil	Influenza	Roche	2020
Tazverik	Tazemetostat	Follicular lymphoma	Eisai	2020
Cibinqo	Abrocitinib	Atopic dermatitis	Pfizer	2021
Imjudo <sup>2</sup>	Tremelimumab	Hepatocellular carcinoma	AstraZeneca	2022
Cibinqo	Abrocitinib	Refractory atopic dermatitis	Pfizer	2022

1 Batch-to-CM conversion

2 Continuous centrifugation and filtration steps

Recent work from the Massachusetts Institute of Technology illustrates its feasibility, with its pharmacy on demand [7], where an end-to-end CM portable refrigerator-sized plant was implemented to manufacture ciprofloxacin. This portable plant consistently achieved drug substance specifications in a fully automated process and with a four-fold increase in the process throughput over its previous iteration. Going up in scale, in a CONTINUUS Pharmaceuticals and MIT collaboration, an end-to-end, QbD-driven integrated continuous manufacturing (ICM) pilot plant [8] was designed to produce both small molecule active pharmaceutical ingredient (API) and oral solid dosages. In 2021, CONTINUUS Pharmaceuticals secured a \$69.3 million government contract to set up the first FDA-approved end-to-end continuous production facility using its ICM technology [9].

### COMPETITIVENESS DRIVERS FOR CM ADOPTION

Drug manufacturing is still mostly based on the traditional batch approach, for both branded and off-patent manufacturers, through a process of a consecutive number of stepwise unit operations. This entails building a large industrial unit, which requires an investment on the order of billions of dollars for complex equipment and several support systems as well as a large space for controlled storage for raw materials and product intermediates and final product. Additionally, because a large workforce is needed to handle the multiple process and transfer steps, increased risk is introduced for the possibility of contamination and errors [10].



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Table 2: CM advantages [11].

Category	Advantages	Description
Cost	Reduced floor space and capex/opex costs	A combination of multistep equipment and quality control PAT tools in a single room with dedicated utilities significantly reduces the required capital and operational costs (capex and opex) as well as floor space and product storage needs, with expected savings of about 70% [11, 12].
Capacity/Quality/Speed	Real-time quality assurance and improved engineered and automation systems	A combination of engineering and automation systems with appropriate control strategy enables monitoring and controlling process parameters in real-time, ensuring that critical process parameters (CPPs) remain within the specified design space. This will ultimately improve productivity, efficiency, and the quality of the final product using a QbD approach to manufacturing [10].
Flexibility/Capacity	Process line flexibility and reduced scale-out/scaleup efforts	CM lines can easily be used to promptly develop and produce several new products or as dedicated lines that operate on an annual basis for a specific product with adjustable throughput depending on demand. The flexibility allows the introduction of extra steps, if needed, and makes process development and scaleup more agile. Furthermore, although scaling up may introduce unwanted risk, a scale-out approach which is well-suited for integration with CM elements may be a beneficial time- and cost-reducing strategy [13].
Speed/Cost	Effect on the supply chain	Supply chains for batch-based processes are lengthy and complex and sometimes involve external partners such as contract development and manufacturing organizations (CDMOs). Simplifying the supply chain by reducing storage, negligible intermediates' shipping costs, and a product delivered in "one-stop shop" fashion will allow more cost-effective decision-making. For example, decisions between the transition from phase II to phase III, which require a significantly increased amount of API material to be manufactured before phase II results become available. Having that capacity flexibility can help avoid investments in unneeded equipment and avoid entrance delays into the market, both of which could result in loss of revenue.
Operational Flexibility/Capacity	Decentralized manufacturing	Presently, portable end-to-end CM plants are not a widespread reality, but have been proven possible [7, 8]. This decentralized portability with small environmental footprint allows shipping and setup to specific environments and locations, requiring only a few square meters of floor space. Portable CM plants, in turn, can be a response to fast-changing demand trends or specific needs (e.g., local epidemics, military use, space travel).
Capacity/Quality	More efficient chemistries	CM of small molecules, at times described as flow chemistry, offers numerous benefits over the traditional synthesis path in batch manufacturing. Through flow chemistry, the possibility of more effective and sustainable synthetic routes become feasible, which were previously difficult to scale up in batch, due to lesser heat exchange demands, better contact with catalysts, more optimized exposure to light, more efficient mixing, and ultimately resulting in higher yields and more sustainable processes (see Figure 1).
Cost	Societal benefits	A positive societal impact is expected with a more ubiquitous presence of CM because it can reduce the cost of drugs and environmental impact, benefiting healthcare and environmental systems, respectively. A broader range of novel dosage forms can be developed for the patients, and even individualized manufacturing, without extensive alterations to the process.
Speed/Quality/Cost	Artificial intelligence	AI implementation lends itself to the full spectrum of pharmaceutical development, from drug discovery to process design and scaleup to the potential prediction of treatment results [14]. This is particularly beneficial for CM, where advanced process control strategies are enabled [15] through the integration of machine learning models, creating a superior monitoring framework in the prediction of progression of a process, trend monitoring, and fault detection and therefore reducing development time, process downtime, and waste [16, 17].
Speed	Approval times	Analysis of submission data has shown that CM applications are approved three months faster than batch applications and reach marketing four months and one month faster after regulatory submission and approval, respectively, allowing patients earlier access to CM products [18].

A process using CM offers several advantages for the pharmaceutical industry and patients, as described in Table 2. Considering the acknowledged advantages to CM, coupled with regulatory agencies beckoning, then the question follows: What is holding back the widespread adoption of CM?

## BARRIERS TO WIDESPREAD ADOPTION OF CM

The pharmaceutical industry has been slower than others in adopting CM. Interest is at an all-time high with slow but steady progress

from an industry application standpoint, but traditional batch production remains the industry's linchpin. Resistance to CM adoption generally falls into one of the following groups [19, 20].

### Equipment

The perception of CM equipment as custom made and not as adaptable as batch equipment has been hindering CM adoption. Traditionally, batch equipment provides impressive flexibility, even though it is limited in design and may have heat and mass

transfer limitations. Another industrywide concern is the robustness of equipment parts, especially replaceable elements, which are heavily used in single-use technology and CM equipment. Additionally, CM requires an increased number of sensors and integrations with equipment to empower automation (see Figure 1). Also considering the rare shutdown of process lines there is a high demand for robust equipment that can endure consistent manufacturing efforts and displace their batch counterparts [21, 22].

Currently, about 80 companies are developing and supplying a variety of pharmaceutical CM equipment to produce small molecules and biologics [23]. Their collaboration with pharma is pivotal to ensure that the many technologies being developed have a standardized and robust design, a cost similar to batch counterparts and, ideally, a plug-and-play functionality.

### Regulatory

One major barrier being identified for this lack of global harmonized guidance is regulatory and scientific standards/requirements [1, 2]. The FDA has been prioritizing advanced manufacturing and adding staff to its Emerging Technology platform, but regulation expectations from other markets (e.g., China and Brazil) can add resistance to approvals. Even if regulators agree, the risk of a delay is enough to break a business case [2, 5]. The lack of more CM-specific guidance for the implementation of ICH Q8 to Q12, which is well-understood for batch manufacturing (BM) [5], coupled with the low-risk-taking nature of the pharma market have inhibited the implementation of novel methods of manufacturing [10].

### Economic

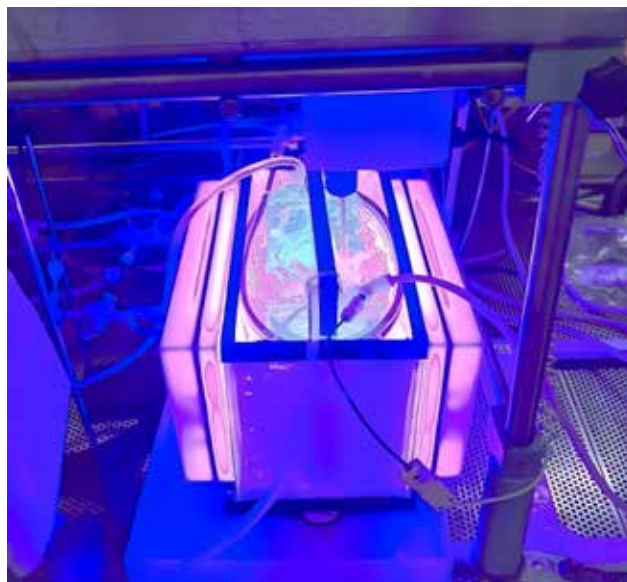
In 2019, the FDA shared data showing that less than 30% of drug ingredients were manufactured in the US because of the labor and cost advantages that offshoring manufacturing to other developing countries offers [9]. As such, major investment is warranted for pharmaceutical companies to fully capitalize on the benefits of CM, and they need to make the hard business choice of investing time and money—with added risk—to widen their manufacturing portfolio versus putting money in established technologies that have been profitable [2].

In September 2022, President Biden signed an Executive Order launching the National Biotechnology and Biomanufacturing Initiative to incentivize and support the development and implementation of advanced manufacturing technologies [25]. These are the type of transforming incentives that pharmaceutical companies need because typically tax and regulatory incentives have been the main drivers affecting cost and time to market. Ireland, Singapore, and Puerto Rico are key pharmaceutical manufacturing hubs where these incentives have had great impact [19].

### Right Mindset, Risk Perception, and Subjectivity/Bias

Mental inertia and risk perception are often points of resistance when adopting new technologies in the manufacturing process.

**Figure 1:** Merck's kilogram-scale, plug flow LED-powered photoreactor (adapted from [24]).



The perception of increased risk by the pharmaceutical companies is skewed, coming from their lack of experience with CM: This is the area where regulatory agencies need to introduce specialized teams to develop regulatory standards, harmonize them with guidelines abroad, and ease the entry of early adopters [19, 26, 27].

Introduction of CM in a company should be treated as a complex and formal project whose scope must include every consideration from people dealing with and contributing to the change process. The life science industry has been slower in adopting CM, and shifting organizational mindsets has been claimed to be the most challenging issue that companies need to overcome. The pharmaceutical quality system (PQS) can only evolve when people feel comfortable in their skillset to make the necessary changes needed to incorporate CM.

### Quality Culture and Specific Skillset

For companies to comply with regulatory expectations, appropriate training plans and corresponding records must be in place. Despite the regulatory obligation, the full potential of CM can only be achieved with a highly skilled and knowledgeable workforce. Data science and engineering has taken a leading role in processing large amounts of data, advanced process modeling, and machine learning that can transform data into knowledge. On the other hand, production engineers and operations on the shop floor need to deeply understand not only the mechanical aspects of the new technology, but also the wider framework and QbD paradigm that underlies most of CM operations. Mathematical algorithms must be validated, and model life cycle management ensures full reliance for quality decisions that ultimately lead to batch release to market.

The pharmaceutical industry has been slower than others in adopting CM. Interest is at an all-time high with slow but steady progress from an industry application standpoint.

Companies have been engaged with their CM equipment and services providers to develop training programs allowing them to import that knowledge. It is understood that the specialization in CM is multidisciplinary and constitutes a revolutionary change from what already exists. Executive management are actively seeking for return on investment (ROI) and a slower learning curve can be a hard sell as an overall business case for CM. Therefore, when planning their next project, companies need to ensure training costs will be included in the business case.

### Generics and Off-Patent Companies

Generics and off-patent pharmaceutical companies—as well as the Association for Accessible Medicines and others—are looking at CM with caution. Two main points of contention are stalling CM adoption in generics production: profit margins for generics companies and ensuring that the implementation of CM does not negatively impact the pharmaceutical market [10].

Typically, pharmaceutical generics companies have low profit margins, making manufacturing cost a pivotal point in why CM is lagging in adoption. These costs are further impacted by the current rising prices of raw materials in the aftermath of SARS-COV-2 pandemic and Europe's geopolitical scenario. Considering the cost associated with transforming existing batch facilities to continuous production facilities, the necessary PAT-related technologies to implement an adequate control strategy, training of highly skilled teams, and lastly the risks and costs associated with new validations and regulatory approvals, help explain why the CM route for branded and generics pharmaceutical companies should be different.

Additionally, it is key for both patients and generics manufacturers that CM-approved drugs can be produced via BM and that CM technology does not prove to be detrimental for the production of a given drug [10].

### Infrastructure

Economic infrastructure—such as telecommunications, transport, and electricity—and social infrastructure—such as water supply and waste treatment systems—are a paramount prerequisite for industrialization and economic development. In developing countries, it is estimated that energy costs are significantly higher, up to three times more than in comparable developing regions: This is mainly due to relying on expensive backup generators as a primary energy source, which adversely affects profit margins and increases the risk to manufacturing due to the possibility of power outages. Furthermore, weak transportation networks will hinder manufacturers' ability to capitalize on regional economies of scale. This lagging in infrastructural development poses a serious challenge to CM implementation [28, 29].

### THE ICH Q9(R1) AND ICH Q13 LOOP – AGILE RISK AND DATA-DRIVEN LIFE CYCLE MANAGEMENT

Many pharma and biopharma companies have been operating with processes in batch mode for their entire history. The quality mindset has grown, with a clear definition of the boundaries of a batch. Therefore, they are in a comfortable position in delimiting the scope of an investigation or a genealogy of a product batch. The introduction of CM has shaken the status quo in relation to the most fundamental quality pillars and an era of quality managers that have been leading the paradigm shift.

Quality risk management (QRM) plays a critical role in ensuring the quality, safety, and efficacy of the products, and its importance has been largely recognized by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), which has included it in several guidelines dedicated to the manufacturing and life cycle management of a pharmaceutical product, namely ICH Q8, Pharmaceutical Development [30], and the more recent ICH Q13, Continuous Manufacturing of Drug Substances and Drug Products [31].

In both cases, QRM is considered a support for the implementation of such guidelines, acting as the handler of information (of the QRM process itself and risk assessment data of the product) and also as a destination of information coming from the development and manufacturing processes in the format of scientific knowledge that should be available for future risk assessment.

This interdependency between guidelines is a well-established concept, driving the holistic product development approach. But some gaps are still experienced in the pharmaceutical industry when it comes to clearly defining how and when to incorporate the risk assessment principles into the product life cycle, and how and when to feed product/process data back into the initial risk assessment. These gaps, combined with the ever-increasing usage and complexity of technology and data in the manufacturing processes, are creating the need to minimize the subjectivity in QRM so that the decision-making process can be supported

by science, data, and knowledge, as well as be robust enough to face any manufacturing process life cycle challenges or regulatory challenges.

A step toward this goal was taken in ICH Q9(R1), Quality Risk Management [32], after the pinpointing of several deficiencies, such as the underlying subjectivity in QRM, supply chain risks, formality of risk assessment, risk-based decisions, and risk review throughout the product life cycle. The ICH Q9(R1) guideline includes new content that should be considered as support for the pharmaceutical industry to start paving the way for the effective adoption of new technologies and digitalization into the QRM process.

### Formality in QRM

ICH Q9(R1) Section 5.1 addresses the level of formality that should be incorporated into a risk assessment exercise by bringing concepts such as formality spectrum, stand-alone QRM reports, and cross-functional QRM teams. Depending on the uncertainty, importance, and complexity of the risk-based decision, the organization should be able to move within this continuum range of formality, with the goal of ensuring a robust risk management. The need to drive this process with structured data and standardized tools is critical, when this newly added section clearly states that “risk scores, ratings and assessments should be based on an appropriate use of evidence, science and knowledge.”

### Risk-Based Decision-Making

ICH Q9(R1) Section 5.2 addresses the risk-based decision-making process as a consequence of the previously defined level of formality, alongside the levels of effort and documentation. Similar to the management of formality, the process of decision-making should also be seen as a flexible set of available tools and rules to be selected based on the importance, complexity, and uncertainty of the decision. Even though it should be a flexible process, it must be supported by a structured program that ensures “the integrity of the data that are used for risk-based decision-making” to promote the understanding of the variables being assessed and thus reduce the level of uncertainty associated with the decision.

### Managing and Minimizing Subjectivity

ICH Q9(R1) Section 5.3 is dedicated to the subjectivity concept that has been part of the ICH Q9 since its initial release. The goal of the revised content is not to eliminate the subjectivity but to ensure that the organizations are aware and recognize its existence in the form of how different stakeholders perceive hazards, harms, and risks. ICH Q9(R1)’s proposal to mitigate the impact of subjectivity is to drive the organizations to “the proper use of QRM tools and maximizing the use of relevant data and sources of knowledge.” Implementing such tools and procedures allows the definition of proper risk scoring scales, standardized risk questions, and the use of existing data to avoid assumptions and biased decisions, increasing the overall robustness of the QRM program.

## The Role of QRM in Addressing Product Availability Risks Arising from Quality/ Manufacturing Issues

ICH Q9(R1) Section 6.1 introduces a new focus around the concepts of supply availability and reliability, which is a critical prerequisite for a CM process. QRM should be used to prevent and mitigate drug shortages by:

- Supporting the design of process monitoring systems, ideally with real-time data, allowing the detection of deviations from the state of control
- Supporting the design of facilities and equipment “through the use of modern technology, such as digitalization, automation, isolation technology, amongst others,” allowing the introduction of concepts such as predictive maintenance, thus reducing the risks to supply chain
- Supporting the qualification of supply chain partners over the product life cycle by effectively monitoring performance

### REGULATORY ICH Q9(R1) AND ICH Q13 DRIVER

The ICH Q9 revision poses itself as an enabler of the ICH Q13 implementation. Because CM processes are highly dependent on robust strategies to manage potential variabilities in product availability as well as quality in equipment performance and in overall output production, having a revised ICH Q9(R1) is creating this regulatory driver to push for the efficient implementation of CM.

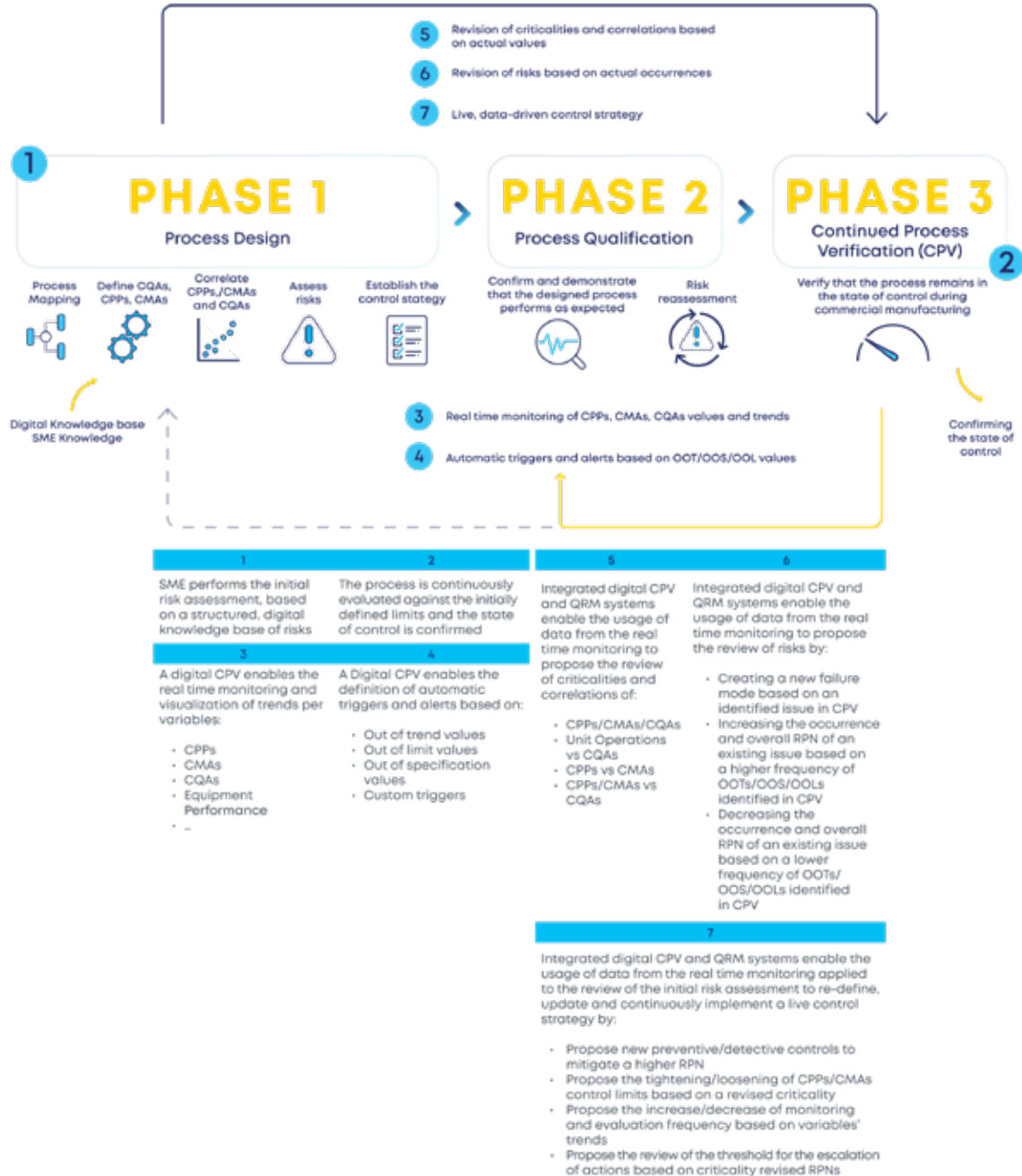
This regulatory ICH Q9(R1) and ICH Q13 driver should work as a two-way channel so that the much-needed agility and flexibility still supported by a robust structure are included in the industry in the entire product life cycle, without knowledge silos and acting as a retrofitting loop between the initial stages risk assessment and the later development and production stages (see Figure 2).

Leveraging this data-driven risk assessment will facilitate the development of a control strategy for CM by improving the understanding and management of concepts described in ICH Q13 such as:

- Process dynamics, where the flexible management of transient events is crucial to maintain a state of control
- Changes in production outputs, where changes in run times, flow rates, or scale demand a robust justification and assessment of risks to update the initially established control strategy
- Process monitoring and control, where in-process material attribute measurements and data analysis methods should be described and justified in the control strategy

Having a structured digital loop (see Figure 2) between risk assessments at initial and late stages of the product life cycle, supported by the ICH Q9(R1) and ICH Q13 guidelines, will enable a faster reassessment of the designed process (phase 1), accommodating changes or observed process trends during production (phase 3). Process design reassessments will be driven by process insights and data, which are then incorporated in a predefined formal

**Figure 2:** Benefits of a structured digital loop for continuous process verification (CPV), supported by the ICH Q9(R1) and ICH Q13 regulatory package. This retrofit can be implemented in any stage between initial and late stages of the product life cycle.



structure (loop back from phase 3 to phase 2 or phase 1). This retrofitting loop enables the expected formal flexibility, a critical concept for an efficient CM process.

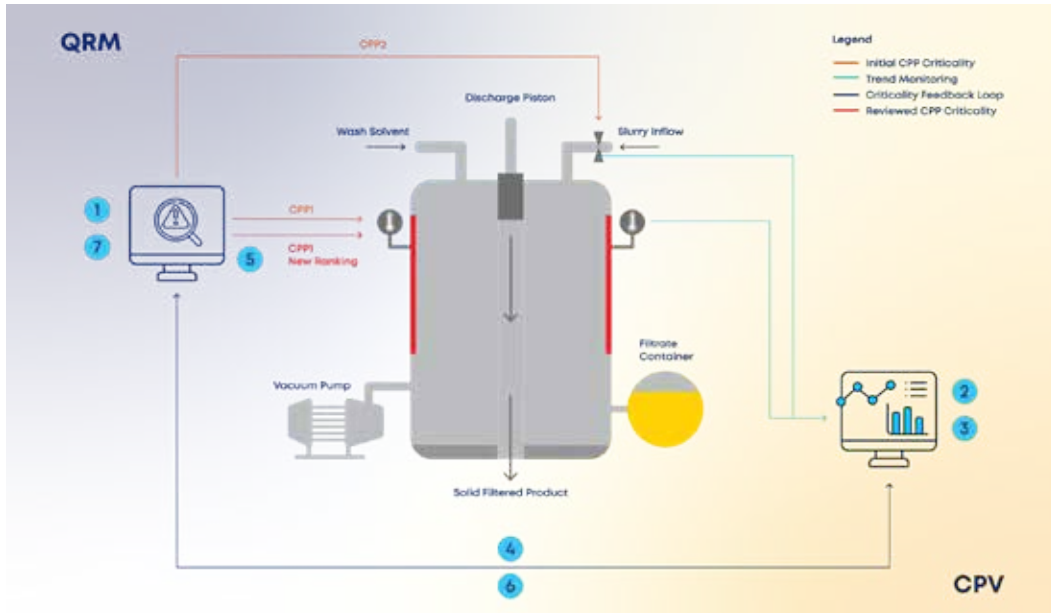
With the new and revised guidance on how to manage data and knowledge about risks and process insights, the proposed loop between the several stages of a product life cycle has gained an increased support in practical application cases. For the sake of

simplification, and illustration purposes, the example in Figure 3 covers a single unit operation (continuous filtration).

In a real-life scenario, this would be applied to the whole process. It is shown that, based on a risk assessment performed prior to phase 3 (1), critical process parameters, critical material attributes, and critical quality attributes have been defined for the continuous filtration step. Failure mode effect analysis was used for



**Figure 3:** Example demonstrating the benefits of having a structured digital loop for CPV, supported by the ICH Q9(R1) and ICH Q13 regulatory package. This retrofit can be implemented in any stage between initial and late stages of the product life cycle.



Filtration example demonstrating the structured digital loop for CPV:						
1	2	5	6	7		
<p>With interlinked risk tools, the initial study defines:</p> <ul style="list-style-type: none"> <li>- Unit Operation: Filtration</li> <li>- Equipment: Vacuum filter</li> <li>- CPP 1: Equipment Temperature</li> <li>- CPP 2: Run time</li> <li>- CMA: Particle Shape</li> <li>- CQA: Residual Solvent</li> </ul> <p>Based on existing knowledge, no critical correlation was established between Equipment Temperature and Residual Solvent for the desired Run Time, no critical risk was defined at the FMEA and the control strategy included the corresponding limits and controls without any further planned action.</p>		<p>With the integrated digital CPV and QRM systems, the following triggers were generated to the QRM team:</p> <ul style="list-style-type: none"> <li>- Revise the initial risk assessment and increase the CPP 1 Equipment Temperature criticality ranking based on the potential OOL for a higher "Run Time"</li> <li>- Revise the Cause-Effect Matrix and establish a critical correlation between CPP 1 and CPP 2</li> <li>- Revise the Cause-Effect Matrix and establish a critical correlation between CPP 1 and CQA</li> <li>- Revise the FMEA and include a new Failure modes for CPP 1/CQA and CPP 2/CQA based on the existing two OOTs</li> <li>- Define new preventive and detective controls for the newly added failure modes</li> <li>- Update the control strategy for the monitoring of CPP 1 with tighter limits, increased monitoring frequency and new preventive/detective controls</li> </ul>				
<p>With the digital CPV, the following data was obtained:</p> <ul style="list-style-type: none"> <li>- CPP 1: Equipment temperature trend within the control limits for the entire run time, but with an increasing trend</li> <li>- CPP 1 vs CPP 2: trigger to update correlation based on data generated and/or OOT</li> <li>- CPP 1 vs CQA: criticality updated based on OOT</li> <li>- CQA: Two OOT Residual Solvent values were detected, triggering two alarms</li> </ul>		<p>Data-driven risk re-assessments allow a continuous preventive refinement of the control strategy in a agile fashion, playing a fundamental role in the improvement of process control</p>				

that purpose, and no critical risks have been identified for this unit operation. As the process enters phase 3, data is continuously gathered and analyzed (3). This data unlocks additional process knowledge which indicates that the defined risk level for the unit operation should be revised based on out of trend (OOT) values that are observed during routine manufacturing.

In a manufacturing context, QRM activities and continuous process verification (CPV) are digitally integrated in a retrofitting loop, which dynamically triggers the risk assessment revision (4), with a consequent effect on the refinement of process control strategy (5, 6, and 7). Risk is thus continuously evaluated based on

actual process data and knowledge and process control strategy fine-tuning is performed on a continuous fashion, creating the much-needed process robustness that works as a CM enabler. Additionally, the use of a digitally setup program of QRM and CPV allows data and knowledge to be gathered from the process and then used as support and justification for any proposed process changes, if applicable.

The current industry approach to risk assessment is static in the majority of cases, with risk assessment exercises being executed or revisited at certain defined process life cycle milestones (e.g., prior to PPQ, prior to commercial manufacturing). The value

of continuously refining risks based on evidence as part of the ongoing process verification is enormous. The gains are easily picturable: increased process knowledge and increased process control, which consequently reduce OOT and out of specification (OOS) results, financial losses, and compliance risks by approaching the process life cycle with a preventive mindset anchored in robust digital strategies.

### REDUCING SUBJECTIVITY FOR QUALITY DECISIONS

The PQS dictates the ruling principles for quality management within a company where, at a lower level, standard operating procedures and checklists break down those principles into actionable items to batch quality assessment.

The ICH Q9 (R1) guideline opens new horizons in how companies can tackle subjectivity in risk management. Any batch needs to go through a series of quality checks to ensure its safety and efficacy before it can be released for human use. Some of the quality assurance decisions are risk based, highlighting the importance of establishing a systematic approach to risk management where data plays a critical role in increasing process understanding and reducing uncertainty.

### CPV and Control Strategy

Far more than conformity against the process range limit or a material specification, a CPV plan, based on sufficient historical data, with a built-in risk to evidence mechanism must be considered as a vehicle to attain such higher levels of quality assurance. Holistic multivariate analysis of the quality attributes of raw material, in-process control, and final product should be a verification point for batch release, including analytical data that goes beyond the formal product specification and that can be a source of valuable insights for verification of state of control.

Subjectivity can also be of concern with material traceability and segregation as well as evaluating the impact of quality planned and unplanned events. Quality decision for automatic segregation of material at risk of nonconformity is governed by automated mechanisms that are driven by instrumentation that acquires and interprets the data using process modeling. The modeling can be validated to ensure not only that the product is within spec when returning to a stationary state, but also how the disturbance affects the operations downstream. Batch genealogy is dynamic because at any point in time a mixture of batches can become components of the final product in proportions that may be estimated. Assessing batch genealogy and material traceability is not deterministic but rather is based on risk, which is refined as more data is generated and process knowledge is increased.

### Cleaning Process

A cleaning process is paramount in designing an adequate CM procedure, and an end-to-end risk analysis should be carried out (from input cleaning solutions and sanitizing agents to the analysis of the rinse and swab samples). The traditional way to see

cleaning as a “black box”—where what matters is the result of the process—is no longer enough.

Cleaning is a planned event that should occur as infrequently as possible to maximize overall equipment effectiveness. Therefore, the number of batches of product that contacts the equipment surface between two cleaning events is greater when compared to batch mode, even when applying a less conservative non-cleaning program in BM. Risk management workflows and the appropriate tools should be selected to assess the criticality of cleaning process parameters, and cleaning quality assurance should be considered similarly to the manufacturing process.

Having equipment sensors for cleaning process data acquisition and analysis that have the ability to link data to previously identified risks is paramount for a continual risk management cycle and to improve the cleaning process. It will also minimize the risk of a cleaning issue that, in CM, can have dramatic effects in the quantity of product with compromised quality: for example, of an undetected cleaning issue in a previous cleaning cycle.

### Quality Investigations

The investigation of quality events in a CM environment brings a new set of challenges when compared to BM due to increased complexity in technology. As such, companies should build their foundations to ensure that batch quality impact assessment and root cause analysis run as smooth as possible. To accomplish this, companies need:

- A multidisciplinary team that is highly skilled with this technology (this may be scarce in some companies)
- A strong QRM foundation, coupled with the availability of data (in the scope of quality investigation, it can support the determination of criticality of the investigation and/or the definition of the scope of the product or potentially impacted systems)
- Digital and subject matter expert (SME) knowledge from similar products manufactured under CM can play a detrimental role, particularly in a context of early adoption

Due to the continuous nature of CM, the number of batches that can be potentially impacted by a quality investigation can be higher when compared with BM. This is the case when a retrospective quality impact assessment needs to be performed with batches that were already quality released.


### CONCLUSION

Despite the current roadblocks to the implementation of CM, there have been clear signs from the different players (e.g., regulatory, equipment manufacturers, academia, governmental entities, among others) in the continued investment in technology. This is expected to rise in the coming years, with the focus shifting toward high-value biologics.

To fulfill all CM potential in process development speed, scalability, and manufacturing throughput, PQSs of pharma and biopharma companies must be restructured on CM's fundamental pillars in product quality assurance. CM brings a myriad of opportunities, and

a clear commitment by the company needs to be made for a product manufactured with this strategy. Companies need to engage in formal change management programs covering people, technology, and processes to support a business case focused on an economically viable ROI for the company.

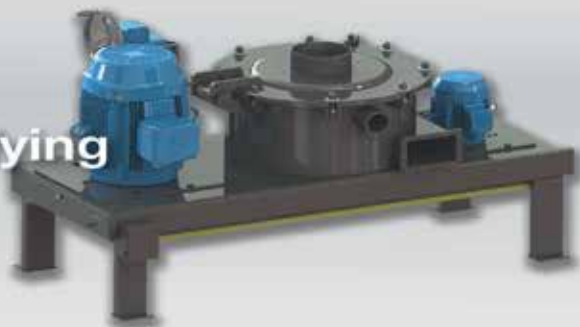
As mentioned, the current industry approach to risk assessment is static. Typically, risk assessment exercises are executed or revisited at certain defined process life cycle milestones. The value of continuously refining risks based on evidence is substantial by approaching the process life cycle with a preventive mindset anchored in robust digital strategies. Leveraging the ICH Q9(R1) and ICH Q13 regulatory package into a structured digital loop that integrates digital process data acquisition (in this article, a CPV example is provided) and QRM systems will drive agile revision of the existing process risk assessment and, potentially, of the control strategy.

Process control strategy refinement will be driven by process insights and data, which are then incorporated in a predefined formal structure. This retrofitting loop between process knowledge and dynamic QRM strategies should be rooted within the company's PQS, enabling the expected formal flexibility, and reducing subjectivity for quality decisions that, in the end, will guarantee the safety and efficacy of the final product, both critical concepts for an efficient CM process. 

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# A SYSTEMWIDE APPROACH to Managing the Risks of Continuous Manufacturing

By Clifford Rossi, PhD

Understanding and managing risks to continuous manufacturing (CM) technology is central to any decision to greenlight CM in a production-ready environment. Applying a systemwide risk management (SRM) approach to manufacturing is essential to ensuring manufacturing projects are vetted in a comprehensive and consistent manner.

Advanced technologies such as CM have the potential to greatly transform pharmaceutical production processes by improving drug quality and supply continuity for consumers worldwide while benefiting the company's bottom line. For much of the pharmaceutical industry, batch manufacturing (BM) processes that have been relied upon for decades remain the preferred approach for most oral solid dosage (OSD) drug products. Considerable uncertainty exists, however, among manufacturers regarding the costs and benefits of CM technology, including several risks that, so far, are holding companies back from making the leap to CM.

Understanding and managing these risks is central to any decision to greenlight CM in a production-ready environment. Although much focus by industry and regulatory authorities remains on manufacturing quality, and rightly so, a host of other major risks must be managed, including financial, investment, operational, environmental, regulatory, supply chain, legal, and strategic risks. These risks tend to be managed separately, but in most cases, are integrated. Applying an SRM approach to manufacturing is essential to ensuring manufacturing projects are vetted in a comprehensive and consistent manner.

Although guidance such as ICH Q9 on quality risk management (QRM) provides a roadmap for the framework and activities to be employed in managing manufacturing quality, these principles need to be broadened and applied across the spectrum of

risks that collectively can adversely affect existing manufacturing activities as well as new manufacturing projects. For example, significant cost uncertainty surrounds the use of CM over BM processes, and though this is technically not a manufacturing quality issue, it directly factors into whether to invest in CM or not.

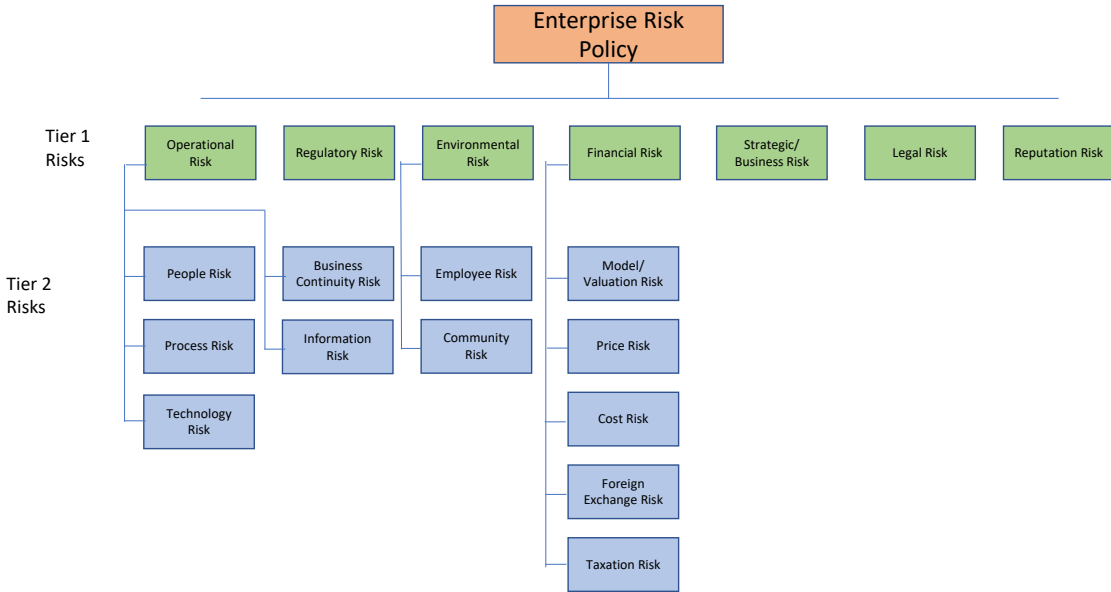
That outcome can affect manufacturing quality if, as a considerable body of research suggests, CM improves quality and operational efficiency while lowering manufacturing downtimes, product defect rates, and scrap costs. Financial risk, therefore, must be incorporated into the calculus of CM investment decisions, along with other risks not directly tied to quality management. This is where an SRM capability is required.

## LEVERAGING SRM CONCEPTS FOR CM

SRM provides a formalized structure about the way in which a company manages its various risks. That structure allows for a consistent approach to identify, measure, report, and mitigate risks, not only for a business line or manufacturing site, but evenly across other activities of a company, such as clinical trial processes. It is conducted at both the macro (enterprise) and the micro level (business unit and even product) and relies on both qualitative and quantitative assessments of risk to the organization. For years, depository institutions such as commercial banks, operating in a highly regulated environment like the pharmaceutical industry, have been held to a high standard in managing risk at an enterprise level [1].

During the 2008 financial crisis, many firms became insolvent due in part to poor loan manufacturing processes used to originate subprime mortgages that amplified credit risk. The techniques and practices adopted by these companies, referred to as enterprise risk management (ERM), can easily be adapted for assessing pharmaceutical manufacturing risk. NASA, for example, leverages many of these concepts in their risk-informed decision-making process (RIDM) for spaceflight programs [2].

Figure 1: Illustrative CM risk taxonomy.



The SRM risk assessment process is only as strong as the underlying risk culture and governance practices of the company. In the banking sector, roles and responsibilities are well-specified in the form of the three lines of defense (3LoD) doctrine. The business area represents the first line of defense and by virtue of its role in managing the profitability and performance of their business is accountable in the first instance for managing its risk.

The second line of defense is represented by a corporate risk function that oversees and provides overarching guidance about risk management for the firm. The company’s internal audit function, representing the third line of defense, ensures that the practices and controls implemented by the other two lines of defense are valid and appropriate. In the context of a CM project, the business unit would be responsible for conducting the manufacturing risk assessment for CM project feasibility with review and verification by the corporate risk second line team.

One of the most important components of SRM is the company’s risk appetite statement. This document is approved by the firm’s board of directors and sets the tone for risk-taking at the company by key risks and setting risk tolerances for how much risk the board is willing to take across all business activities. For pharmaceutical manufacturing, ensuring drug products meet or exceed “safe and effective” standards of quality is a prerequisite. Beyond that standard, risks encountered in the manufacturing process should have a risk appetite statement associated with it commensurate with the risk tolerance of the board. A companion to the risk appetite statement is the risk taxonomy. This document catalogs and summarizes the various risks to the company. A list of key risks associated with CM that would require a risk assessment is shown in Figure 1.

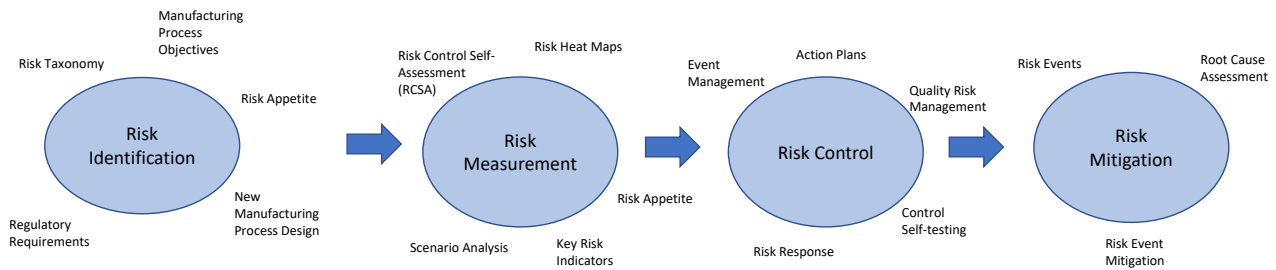
Risks can be differentiated between primary (Tier 1) and secondary (Tier 2) risks. One of the greatest risks pharmaceutical manufacturing faces is operational risk, which can lead to reductions in profitability and higher costs, and impose other risks on firms. Operational risk is associated with deficiencies in process, people, or technology or external events that have adverse financial and nonfinancial consequences for the organization.

In the case of pharmaceutical manufacturing, operational risk can manifest in the form of underlying process weaknesses (e.g., deficiencies in standard operating procedures) that lead to product contamination, higher scrap rates, greater risk of environmental hazards and employee safety risk, manufacturing downtimes, and longer processing periods than desired. These outcomes, in turn, raise the firm’s costs and/or expose it to potential regulatory scrutiny as well, which brings its own set of risks. Companies that can objectively compare BM vs. CM processes considering these factors are in a better position to understand how manufacturing quality can lead to improved financial and nonfinancial outcomes.

Operational risk is usually a catalyst for other primary risks. Risks tend to cascade once an event has unfolded as happened to banks with poor loan manufacturing processes. Operational risk was a catalyst leading to a credit and liquidity risk crisis at many banks in 2008, eventually posing enormous regulatory, legal, and reputation risk to those firms with poor operational controls. The same is true for pharmaceutical manufacturing where a drug recall today due to any number of operational factors can become tomorrow’s headline and regulatory risks.

For example, a recall in 2008 of the widely used blood thinning drug heparin occurred due to an adulteration of the manufacturing

Figure 2: SRM risk management assessment process.



process that introduced oversulfated chondroitin sulfate (OSCS) into batches of the product from a manufacturing facility in China. It led to many severe reactions to heparin in the U.S. and some deaths. Although an isolated event, considering the vast numbers of OSD products manufactured each year, the heparin recall stands out as a cautionary tale for the importance of quality in pharmaceutical production and operational risk management capabilities.

The risk appetite statement should in turn be driven to each line of business with key risk indicators (KRIs) developed for important risks to be managed for that year. Ideally, those risks should be quantified in some fashion and used in setting employee incentive compensation plans. At the business unit level, the risk appetite approach could be leveraged in product development and new initiatives such as manufacturing technology investments. A formal risk assessment process should be integrated into the CM evaluation process.

## DEVELOPING A ROBUST RISK ASSESSMENT PROCESS FOR CM TECHNOLOGY

Adoption of CM technology in pharmaceutical manufacturing has elements of both risk and uncertainty. Distinguishing between them is critical to how companies approach risk management. According to Knight, risk management is not knowing the outcome from an action in advance; rather it's having the ability to reasonably measure its likelihood. More formally, there are both a priori and statistical probabilities that provide a means of assessing risk [3].

An example of an a priori probability is the mathematical representation of a distribution of product defect rates over a period. Some aspects of pharmaceutical manufacturing processes and QRM controls and assessment lend themselves to quantifiable measurement of risks, such as operational failures and/or quality defects, based on actual manufacturing data with existing technology. However, limited experience and data associated with CM in the pharmaceutical industry in general presents several challenges in measuring key risks in this manner for which another approach to risk assessment is required. This is exactly where a robust SRM process can guide the CM evaluation process.

The general SRM framework is depicted in Figure 2. A sequence of four major risk activities comprise the risk assessment process. It

starts with identifying all the risks associated with a CM initiative. Determining the specific objectives of the project (e.g., establishing a new facility for new products, expanding manufacturing capability of existing products, or replacing an existing batch process for current products) along with mapping out the new CM process from end to end, is required to highlight any potential risks associated with the new technology.

Developing a catalog of all risks associated with the CM process, as illustrated in Figure 1, is essential during this phase to ensure each risk lies within the firm's risk appetite. The process is dynamic with a built-in feedback mechanism. Should issues or events arise over time, a root cause analysis (RCA) would be used to identify what happened and provide recommendations on mitigating such occurrences in the future.

A precursor to measuring any risk associated with CM is the development of a risk profile. Any new process such as CM invariably exposes the company to inherent risk, which is defined as the uncontrolled risk of some form associated with the new process. An example of an inherent CM risk would be the lack of staff that has experience operating the CM process, which could lead to delays in production schedules. The inherent risk for each risk type identified in the CM risk taxonomy would need to be evaluated.

Once inherent risks are identified and evaluated, controls to ensure each risk remains within the firm's risk appetite would be developed. An example of a control to mitigate the inherent risk of supply shortages of skilled CM operators might be the introduction of a formal CM training program for all manufacturing operators. A final assessment of post-control risk, referred to as residual risk, accompanies the risk profile. If post-control residual risk remains too high, a further reassessment of any additional controls needed to reduce it to expected levels would be conducted.

The assessment of inherent and residual risk requires some determination of the likelihood of a risk, the possible severity, and any impact that would follow should it occur. Overall risk, typically measured in dollars of loss or costs to the firm, is defined as the product of a risk's likelihood and severity. For example, probability distributions of incurring defects in BM and CM processes could be generated and used in conjunction with a defined risk



tolerance (e.g., 99.5% confident of a defect rate < x% over a specified period of time) to assess manufacturing alternatives against a specific risk type (e.g., process risk). Likewise, the severity of such outcomes can be derived from actual or simulated data.

In the absence of empirical data on which to develop a reliable quantitative estimate of both components of some risks (e.g., people risk), heat maps are commonly used tools in many industries, including banking, especially to assess operational risk for rank ordering the likelihood and severity of a risk outcome and to provide an overall rating (red = very high risk, green = very low risk), as shown in Figure 3.

A heat map is flexible, allowing variation in the number of risk categories as well as the criteria for what defines each rating. In terms of assessing the likelihood of a risk, it is important to provide some general guidance of what distinguishes one risk rating from another. In Figure 3, for instance, a very low likelihood rating might represent those risks that occur less than 5% of the time. Such criteria are typically determined jointly between business and risk teams based on experience and judgment.

Factors that could be used in assessing the likelihood of a particular risk associated with CM might include the complexity of the process and technology. One of the touted benefits of CM is the degree of automation, which can potentially reduce manual intervention in the process and enable more seamless processing. That could very well reduce the likelihood of operational breakdowns as compared with batch processing.

Other potential considerations in assessing the likelihood of a risk associated with CM technology might be workforce experience level, competency, and CM labor supply. The likelihood that the supply of well-trained CM manufacturing operators may not be sufficient to ensure operation of a CM manufacturing facility would need to be determined and slotted into the appropriate likelihood risk rating.

The impact rating for a risk would take on a similar approach. In this case, the impact of a risk occurring can be multifaceted. A production stoppage could cost the firm lost revenues and/or costs associated with a breach of a service level agreement with a business counterparty, or potential legal and or regulatory costs, or reputation effects, for example. For each impact category some criteria should be established to differentiate each risk rating.

Consider the example of an unexpected shutdown during the manufacturing process. Events that pose losses of \$1 million or less might be considered negligible impact, whereas those generating over \$50 million might pose an extreme impact to the business. Although these figures are illustrative only, each company's experience with risk events, the risk impact, and the company's risk appetite would be essential in setting these risk thresholds.

Once likelihood and impact risk ratings have been developed for each CM risk, a final overall risk rating can be developed by combining both ratings. Figure 3 presents a 5x5 matrix for assigning final overall ratings. One way to determine those final ratings is to apply a numeric score shown to each of the five likelihood and five severity ratings. A rating of very low risk or negligible might,

Figure 3: Illustrative heat map for assessing less quantifiable risks.

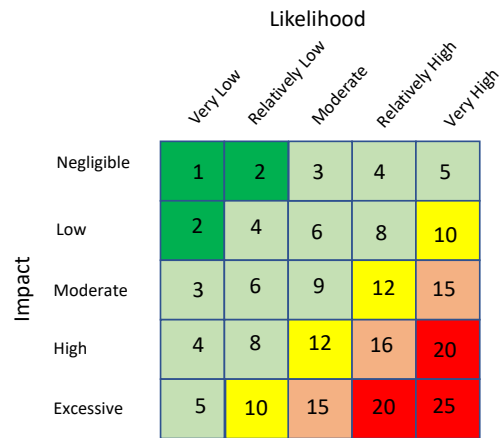


Table 1: Illustrative CM risk ratings.

Risk Rating	Total Points
Very high	≥ 20
Relatively high	13–19
Moderate	10–12
Relatively low	3–9
Very low	≤ 2

for instance, receive a score of 1, whereas very high or excessive risk might be assigned a score of 5. Then a simple multiplication of likelihood and severity ratings could be lined up against score thresholds for each overall rating. Applying this simple example, overall ratings would be classified based on score, as shown in Table 1.

These inherent risk ratings would be evaluated against various risk responses to bring the overall residual risk in alignment with the company's risk appetite. Risk responses are either accept, avoid, reduce, or share. Controls would be established (e.g., CM standard operating procedures) to ensure that the final residual risk rating is at the appropriate level for that risk.

Once a CM project has been approved, ongoing assessment of plant performance is necessary. This is where both a set of KRIs and risk control self-assessments (RCSAs) become essential. KRIs provide ongoing benchmarks of performance around specific project risks. Commonly used quality metrics in place today could be suitable KRIs for managing process and technology risk. The percentage of manufacturing operators certified in QRM or other technical proficiency training could serve as a form of people risk KRI, for example.

KRIs for other risks such as financial performance or regulatory risk would be developed as well. Whatever KRIs are used should be

actionable, transparent, replicable, and consistent across business processes. RCSAs, on the other hand, provide a periodic mechanism to track and prioritize emerging issues and risks, and establish remediation plans where appropriate and identify accountable parties. RCSA templates should be consistent across business areas to help manage operational risks across the company.

Manufacturing process QRM is an integral component of the overall risk management assessment framework. For years, pharmaceutical manufacturers have built these processes to conform with current good manufacturing practice (cGMP) [4] regulations as well as various ICH quality standards such as ICH Q9 and Q10 [5] and now Q13 [6] for CM processes. Quality control lies at the heart of any robust risk management process, enabling firms to proactively identify process weaknesses and remediate them before they turn into a risk event. The FDA's Quality Management Maturity (QMM) and Quality Metrics programs are the next evolution for companies to elevate their quality management programs [7].

A number of industries also use expert scorecard tools to assess manufacturing quality including aerospace and automobile manufacturers. Building this capability into the risk management process for new technologies like CM establishes a critical control point for monitoring CM system performance.

## SIMULATION ANALYSIS TO EVALUATE CM TECHNOLOGY VIABILITY

An ongoing challenge in the application of SRM is obtaining robust estimates of key risks where empirical data are limited, especially for assessing new manufacturing technologies. Given the lack of extensive historical CM investment and of financial and engineering operating data in pharmaceutical manufacturing, relying on a single set of best estimates to determine financial feasibility and risk of CM technology is insufficient. This is where simulation analysis can provide a more robust set of estimates of CM technical and financial performance over time by varying different key assumptions.

### Net Present Value

Pharmaceutical manufacturers face a variety of financial risks. Financial risk in this context is defined as the shortfall in cash flow that arises from factors that affect firm profitability. Net cash flow, or net operating income (NOI), is defined as the dollar amount of cash inflows less cash outflows over some period, such as a year. Cash inflows are defined as all sources of revenues (R), such as from pharmaceutical sales, whereas cash outflows could include costs of goods sold (COGS), taxes (T), costs of hedging foreign exchange (HC) for a global pharma manufacturer, depreciation (D), research and development costs (R&D), and general and administrative costs (G&A). NOI is more formally defined as:

$$NOI = R - COGS - G\&A - D - T - R\&D - HC$$

Companies deciding whether a project is financially viable often rely on a single scenario: multiperiod discounted net

present value (NPV) analysis or its variants. Traditionally, NPV analyses are performed in a deterministic manner, i.e., without any degree of uncertainty introduced.

NPV in this form can further be defined as follows:

$$NPV = \sum_{t=1}^T \frac{(Revenue_t - MOpEx_t^{\Delta} - NMOpEx_t - hc)(1 - MTR_t)}{(1 + r)^t} - MCapEx_0^{\Delta}$$

where:

- Revenue represents annual sales of the pharmaceutical OSD product
- MOpEx is manufacturing operating expense for technology a (i.e., BM or CM)
- NMOpex is nonmanufacturing annual costs
- hc represents foreign exchange hedging costs
- MTR is the marginal corporate tax rate for country i
- MCapEx is the capital cost associated with technology a
- r is the discount rate

Investment projects are viable if they are NPV positive.

### Variability of NPV

Variability of NPV gives rise to financial risk. In the case of a firm's financial risk, a company is concerned about having a project generate sufficient cash inflows to satisfactorily cover cash outflows over some time with a certain degree of confidence. However, endogenous or exogenous factors can introduce a degree of uncertainty into the NPV analysis. The nature of the product life cycle in the pharma industry contributes to cash flow variability in several ways.

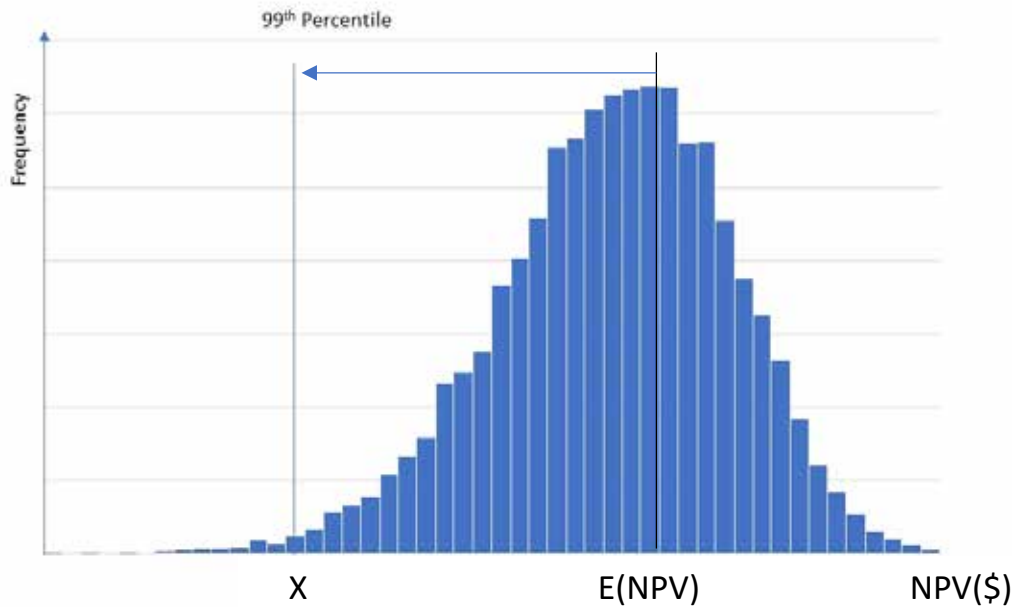
For example, product pricing and sales fall once the product moves from having brand protection to generic status. Engineering cost uncertainty presents another source of financial risk to pharma manufacturers. From the standpoint of investing in advanced manufacturing technology, where limited hard data on investment and operating costs exists, companies need to consider upfront and ongoing cost uncertainty associated with new processes that do not have established track records in the industry.

This cost uncertainty can lessen interest in advanced technologies such as CM over standard batch technology, which has more extensive application in the industry. Simulation of financial outcomes over a range of possible and less likely outcomes can reduce this analytical challenge for CM and boost confidence in such projects' results for estimating project feasibility compared to BM.

### NPV value-at-risk

To illustrate this concept, assume that a company has determined that for any project it wants to be 99% confident that it will be NPV positive. The histogram in Figure 4 represents a discrete distribution of NPV outcomes for a company over a project's life. On average, this company could expect to see an expected NPV amount  $E(NPV)$  that, in a normal year, would be some positive amount. However, depending on market conditions and other factors, a

Figure 4: NPV-at-risk concept.



wide variation in NPV could occur over a year. Drivers of such variability could include changes in the amount of sales and/or unit pricing due to changes in product demand, degree of competition for a product, or variability in various cost components of NOI.

Given the desired target level of confidence, the firm in this example would want to manage its business in a manner to ensure its NPV does not fall below the level of X more than 1% of the time. This point would be referred to as the project's NPV value-at-risk (VaR). Most NPV analyses only evaluate a single path of cashflows, which could be misleading if one or more components of NPV has some variability associated with it.

#### Introducing uncertainty into the NPV analysis

A standard way of introducing uncertainty into the NPV analysis is to represent key revenue and cost inputs as stochastic variables. A degree of randomness is introduced in measuring the stochastic variables by way of their standard deviation or volatility. Three stochastic variables were incorporated in the NPV model: revenue, MOpEx, and MCapEx were assumed to follow a generalized Weiner process with a constant drift rate and variance. The discrete form of each stochastic variable is represented by the following:

$$\frac{\Delta V}{V} = \mu \Delta t + \sigma \epsilon \sqrt{\Delta t}$$

$$\Delta V = \mu V \Delta t + \sigma V \epsilon \sqrt{\Delta t}$$

where  $\mu$  is the drift rate,  $\sigma$  is the standard deviation (volatility) of variable V, and  $\epsilon$  is a random normal variable. It is assumed,

following convention with other cost studies, that operating and capital costs are lognormally rather than normally distributed as are revenues [8]. The lognormal distribution ensures nonnegative costs and revenues, and better reflects the tendency that costs are more likely to go up than down.

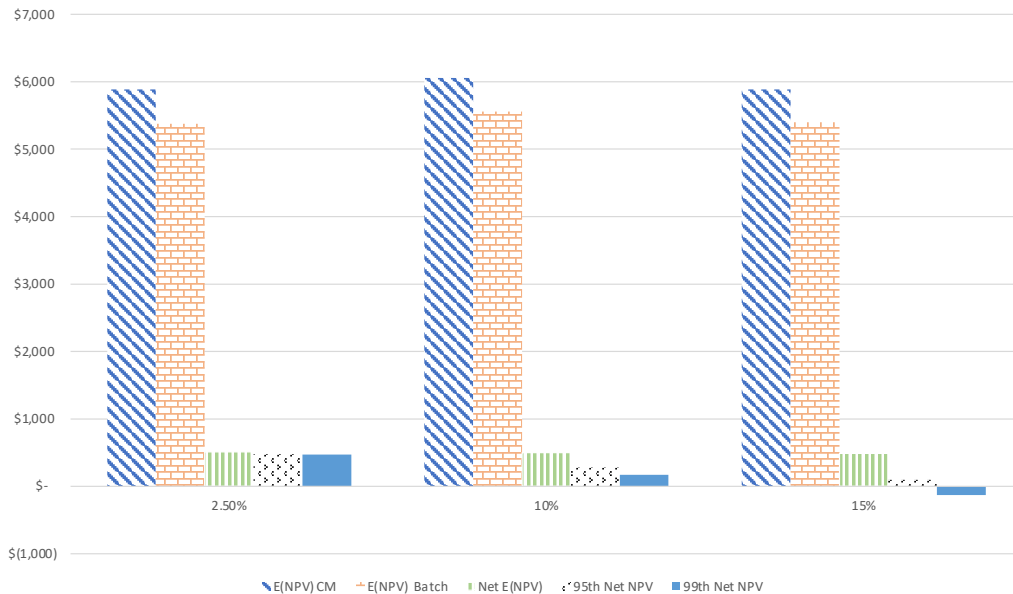
Leveraging historical data augmented by sensitivity analysis of a variable's volatility significantly upgrades a standard deterministic NPV analysis. Evaluating CM under a variety of cost outcomes can therefore provide considerably more confidence in the NPV results, particularly if NPV VaR is applied as a decision rule.

#### Brand vs. generics manufacturing example

To provide more insight on the potential for simulation-based methodologies to assess new manufacturing technologies such as CM, consider some findings from a recent study that developed a stochastic NPV simulation of brand and generics manufacturing for new facilities. NPV distributions of BM and CM processes in different countries [9] were simulated leveraging actual industry financial revenue and cost information, and detailed engineering cost information of CM and CM processes from a seminal manufacturing cost analysis of these two technologies [10]. The analysis considered 156 different domestic and foreign manufacturing scenarios under varying assumptions of revenue and cost uncertainty. The model generated 10,000 different NPVs from which NPV distributions were generated.

Figure 5 provides a summary of the comparison for brand companies deciding whether to manufacture in the U.S. leveraging CM vs. BM technology under three CM capital and operating

Figure 5: Brand company U.S. site technology NPV comparisons by cost volatility scenarios.



cost volatility scenarios. The results suggest that for brand companies, NPV for CM-based technology is greater than that using a batch process across all cost volatility scenarios. Moreover, it should be noted that only under the most extreme cost volatility (i.e., increasing cost volatility by 15%) scenario and most conservative investment threshold (99th percentile) would BM NPV ever exceed CM NPV.

This suggests that, at least for U.S. sites, CM manufacturing should be the preferred technology choice for brand companies. Similar results for generics drug manufacturing as well as manufacturing scenarios for different countries were found and included in the full analysis, demonstrating the applicability and flexibility of simulation of CM technology NPV to a broad range of scenarios.

The benefit of scenario and simulation analysis is that it doesn't rely on one set of financial model inputs. Rather, by generating a distribution of outcomes, it provides a probabilistic assessment of CM project financial performance that can be used to measure the financial risk of the project. By establishing a level of confidence (e.g., 99%) over a specified time horizon for which the project must be NPV positive it creates a consistent methodology that can be applied to other capital investment projects across the enterprise. NPV VaR provides a more conservative benchmark to evaluate projects than simply relying on expected NPV or even single scenario NPV results. This type of analysis is particularly useful for CM projects where uncertainty in key technical production, engineering, and financial parameters may exist.

### EFFECTIVE CM PROCESS RISK MANAGEMENT


For decades, industry sectors such as banking have applied ERM principles in their businesses to assess existing and new products

and services from a risk-adjusted return perspective over the entire product life cycle. ERM is a data- and analytical-driven discipline augmented with business judgment that is essential in today's technology-driven business. Embracing a systemwide view of risk, especially for pharmaceutical manufacturers, enables companies to ensure that risks are managed in a consistent manner by applying standard risk management practices and controls. As pharmaceutical manufacturers consider leveraging CM technologies, SRM should begin to play a large role in that evaluation process, transcending traditional QRM practices by centering on a holistic and integrated approach to risk management across multiple risk types. A benefit from the SRM process is that it is repeatable for any business activity once put in place.

The ingredients of a sound SRM program require board and senior management commitment to risk management, a risk-aware culture, and the risk infrastructure to identify, measure, control, and mitigate risks. Without board and management support, SRM becomes an exercise in futility. Having CM serve as a use case to demonstrate the importance of SRM can cultivate support for it from the top of the organization while enhancing the CM evaluation process. By nature of their business, pharmaceutical companies are more risk-centric than other sectors, such as banking. In that regard, it may be easier to build the internal support and awareness for SRM.

### CONCLUSION

For businesses unfamiliar with SRM principles and benefits, SRM can be viewed as an impediment. However, when properly introduced in a balanced risk-reward manner, SRM is, in fact, an enabler to assure that the company understands the risks it is taking and

establishes clear benchmarks of performance on managing the risks it retains. Pharmaceutical manufacturing finds itself at an important inflection point technologically with the promise of advanced manufacturing capabilities such as CM to improve production quality, operational efficiency, and continuity. Pharmaceutical companies that leverage SRM principles will find this provides a distinct competitive advantage relative to peers in making more informed risk-based decisions not only for manufacturing but across the enterprise. 

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# USP/BIOPHORUM WORKSHOP on Continuous Manufacturing of Biologics

By John F. Kokai-Kun, PhD

In the interest of understanding the current state of continuous manufacturing for biologics and to facilitate the path toward adoption of these promising technologies, the United States Pharmacopeia (USP) and BioPhorum jointly sponsored a hybrid workshop. This article summarizes trends from the workshop and ponders next steps.

Biopharmaceutical continuous manufacturing (BCM) offers many potential advantages over more conventional batch-based manufacturing of biologics [1]. Some advantages are apparent based on the nature of a continuous processing, including higher efficiency at lower cost [1]. Other advantages may not be as readily evident, including the potential for improved product quality due to reduced and more consistent residence times in the bioreactor, the capacity to adjust product quality process parameters during manufacturing, faster time to release of product (which is especially important for labile products like cellular therapies), and reduced facility costs and environmental impact of the process [1–3].

There are also barriers to the adoption of BCM. Some barriers are technical, such as adapting unit operations that are more suited for batch processes to continuous processing (e.g., viral inactivation or bind and elute chromatography) or correctly scaling each step of a process to allow efficient flow from end to end [4, 5]. Other challenges reflect the cautious nature of pharmaceutical manufacturing, like risk aversion and regulatory considerations. Examples of these other challenges include lack of sufficient data to justify hesitancy to change an established manufacturing process or adopt new technology that is not as accepted as existing technologies [6].

The USP/BioPhorum workshop, “Continuous Manufacturing of Biologics: Addressing Barriers to Adoption,” was held 7–8 December 2022 at USP headquarters in Rockville, Maryland [7]. The workshop was attended by participants from industry, academia, the US FDA, and others. It consisted of 18 presentations over two days, with panel discussions at the end of each session. The organizing committee for the workshop included:

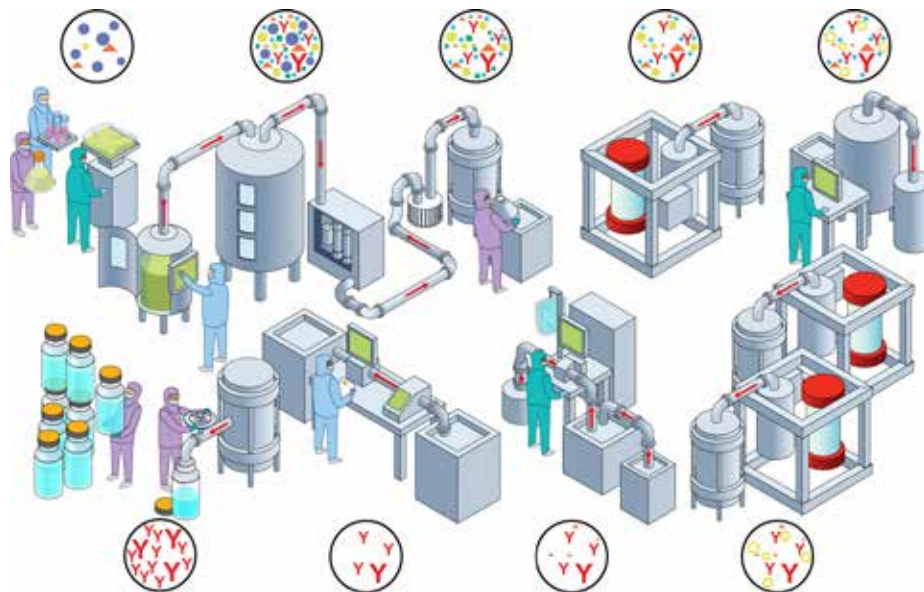
- Rich Chen, Executive Director, Purification & Viral Safety, Eli Lilly and Company
- Chris Hwang, Chief Technology Officer, Transcenta Therapeutics Inc.
- Maura Kibbey, Director, Biologics Marketing, US Pharmacopeia
- John Kokai-Kun, Director, External Scientific Collaboration, US Pharmacopeia
- Julie Kozaili, Senior Scientist, Asahi Kasei Bioprocess
- Graeme Moody, Program Manager, BioPhorum
- Kristina Pleitt, Senior Manager, Bioproduction R&D Innovation, Thermo Fisher Scientific
- Mark Schofield, Senior R&D Manager, Pall Biotech
- Andrew Zydny, Bayard D. Kunkle Chair and Professor of Chemical Engineering, College of Engineering, Pennsylvania State University

Over the course of the workshop, several trends began to emerge from the presentations and panel discussions. This article summarizes those trends and ponders next steps in the adoption of continuous manufacturing of biologics.

## IT'S ALL ABOUT THE PLUMBING

At its most basic level, manufacturing of biologic products involves the movement of various solutions from one vessel to another, through appropriate unit operations that constitute the manufacturing process, in the correct sequence of events [8]. For example, this

**Figure 1:** A typical batch-mode mAb manufacturing process. Circles represent substances found in the production flow stream at each step (reproduced with permission from Mark Verdecia, USP).



could be the filling of a bioreactor with growth media, the collection of eluate eluted from a capture chromatography step, exchanging the buffer of the final bulk drug substance, or flushing a collection tank with cleaning solution following a manufacturing run.

Most bulk biologic drugs begin and end in liquid form, and biologic manufacturing processes are designed to move various liquids into and out of the next receptacle in the process in the correct sequence. Figure 1 illustrates a typical monoclonal antibody production process, showing upstream steps (1–4) and downstream steps (5–12):

1. Seed train/cell expansion
2. N-1 seed bioreactor
3. Production bioreactor
4. Harvest
5. Capture chromatography (Protein A)
6. Low pH viral inactivation
7. Polishing chromatography step 1
8. Polishing chromatography step 2
9. Viral filtration
10. Ultrafiltration/diafiltration (buffer exchange)
11. Final filtration
12. Bulk fill of drug substance: Although this tightly controlled process can be complex in batch manufacturing mode, it is considerably more complicated in a BCM process where, by definition, the product continues to move through the various steps of the process without interruption

Many of the technical challenges associated with designing a BCM process revolve around controlling the continuous flow of the process through each unit operation from beginning to end,

especially when the operations may have different optimal flow rates [1]. Several operations of a typical monoclonal antibody (mAb) purification process are more conducive to discrete start/stop steps than continuous ones (see Figure 1). These operations include bind and elute chromatography and low pH viral inactivation.

How does a process continue to flow from one step to another when there are starts and stops in the process? One solution that was discussed frequently during the workshop was the use of surge tanks between the various operations. Surge tanks between each step of the BCM process store the outflow from a previous step before it enters the next step. This allows the BCM process to accommodate variables like different flow rates for various operations.

Surge tanks can also be used to divert product streams with suspected deficiencies out of the main flow until a determination can be made as to whether to continue to process the material. Kurt Boenning from Pall Corporation presented a strategy for using surge tanks with three-way valves and automated pump speeds to control a model continuous process. In Pall's strategy, the surge tanks are mounted on balances so that the volume of material in the tanks automatically control the pump speeds. The dual inlets on the three-way control valves also allow for automated introduction of either product stream or buffer.

Lara Fernandez Cerezo from Merck & Co. also reported that they use surge tanks to control their processes, linking their downstream flow rate with their upstream processing conditions. Merck is currently conducting GMP runs of a BCM process for mAbs so that they can develop a process that can produce sufficient material for phase 1 clinical trials.

Additional challenges lie in the loading and elution of capture chromatography steps. Various strategies using multiple columns are under development, and some strategies have considered the use of up to four identical columns for such a procedure [1].

Irina Ramos from AstraZeneca discussed the strategy they are developing with Pak BioSolutions for implementing BCM processes, including their use of multicolumn setups and an integrated control system that can operate four continuous purification stages simultaneously. AstraZeneca uses a two-column configuration, which allows one column to be loaded while the other column is being washed, eluted, and regenerated. A key consideration in this strategy is that the load time for the column needs to be longer than the regeneration time to maximize productivity. They also use column guards and sterile filters to safeguard their systems. Microbial control is further ensured by using a closed system that is extensively tested and qualified before it is run.

Other challenges around the efficient movement of products through the production process were also discussed. Filters are frequently used at various points in a process for activities like sterile filtration, particle removal, and viral clearance, but these filters can become clogged and need to be changed. The flow rate of the process needs to be monitored before and after filters to detect fouling of the filters. One strategy discussed to allow the efficient replacement of filters to prevent a process pause is to use a dual flow path system with two filters where the pressure is monitored and when it reaches a set point, the product stream is automatically diverted to the secondary path next filter while the filter in the first path is changed.

Buffer management is also an essential aspect of any biologic process, but this is particularly true for a BCM process. Charlie Heise from Fujifilm Diosynth discussed their MaruX system, which combines upstream productivity with downstream intensity. Specialized manufacturing skids have been developed that allow 5×-concentrated buffers to be diluted inline at the point of use are included in the system. This has resulted in the footprint for buffers being half of what would be expected. Fujifilm's BCM facility will be ready for GMP manufacturing in 2024.

Michael Coolbaugh from Sanofi explained that they use a universal skid for all downstream BCM operations. The design goal is for their flexible and modular process to be plug and play with no need for clean-in-place/sterilize-in-place requirements due to the use of single-use equipment that can be replaced rather than cleaned and sterilized between uses.

Tangential flow filtration (TFF) is a technology frequently used in biologic manufacturing processes to exchange buffer or concentrate the product. John Moomaw from Eli Lilly and Company is developing an integrated continuous counter-current TFF system using single-pass membranes. This technology uses a series of dilution and concentration steps with pumps to control the flow. There can be pressure accumulation and inline mixing challenges but including surge tanks can help alleviate this. Eli Lilly is working toward an automated system for use in BCM to develop a non-GMP TFF pilot skid to include in their BCM development work.

## VIRAL CLEARANCE

Biologics are produced by living organisms, often mammalian cell lines, and these cells can carry known and unknown viruses, some of which are endogenous to the cell line. Viruses can also be introduced by operators or come from other raw materials [9]. It is a requirement of any purification process that it significantly reduces the risk of viruses being found in the final product [10]. Indeed, demonstrating the capability of any process to remove potential viral contamination is an essential part of characterizing the process. This remains true for BCM processes as well, but novel strategies for virus removal and validation of this removal are required.

Scott Lute from the US Food and Drug Administration (FDA) discussed viral safety strategies and how they apply to BCM processes. These include novel strategies to replace the static low pH virus inactivation step used in batch processes (see Figure 1) with technology conducive to continuous flow-through processing. In a conventional batch process, this step generally involves holding the product at a pH of 3.5–4.0 for at least 30 minutes [11].

Strategies to adapt this static operation to BCM include alternating dual-tank strategies or flow-through modules that reproduce the low pH hold step in a continuous loop system allowing for continuous flow. AstraZeneca, guided by Pak BioSolutions, uses a size-exclusion chromatography column to achieve the required low pH “hold” for viral inactivation while maintaining a continuous flow. Important parameters like residence time distribution must be characterized and are often investigated by scale-down modeling, where critical parameters include time, pH, temperature, and adequate mixing of the flow stream for the interactions.

Beyond viral inactivation, viral filtration is also an essential step to ensuring the safety of any bioprocess. Small-scale models are often used to study this important step. Ioana Pintescu from Asahi Kasei Bioprocess presented studies that she performed in collaboration with the FDA to validate viral filters under continuous flow filtration. These studies involved spiking known amounts of virus into various solutions and then examining the capacity of the filters to clear those viruses.

Several parameters needed to be considered when planning these studies, including the stability of the virus over the length of the study and the best strategy for introduction and inline mixing of the spiked virus into the test system. These studies demonstrated that the Planova filtration system could remove 6 log PFU/ml of spiked virus. Hironobu Shirataki from Asahi Kasei Medical Co. expanded on the use of their Planova BioEX filters, including the use of multiple filters from 16- to 35-nm pore size.

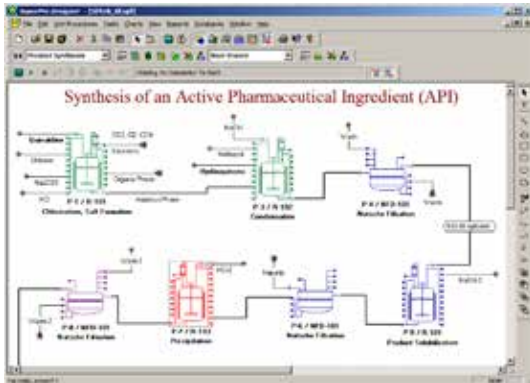
Another aspect of viral clearance discussed is whether it is necessary to physically sequester material and equipment pre- and post-viral filtration. Fujifilm Diosynth's and Transcenta's strategies are to physically segregate potentially virus-positive (pre-filtration) from virus-negative (post-filtration) steps in the process and facility, but Sanofi argues that this defeats one of the advantages of converting existing batch processes and facilities to BCM; that is being able to use existing facilities without having to do substantial renovations.



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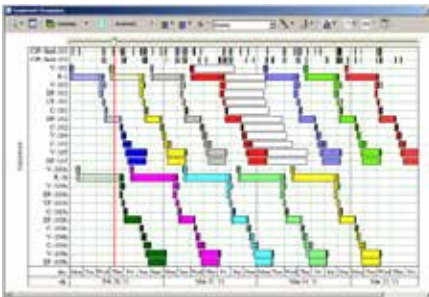


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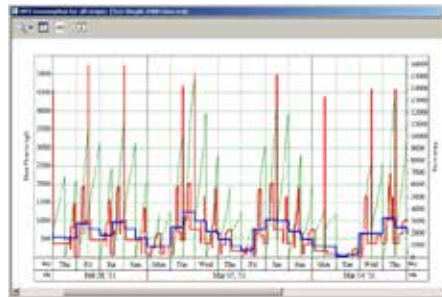
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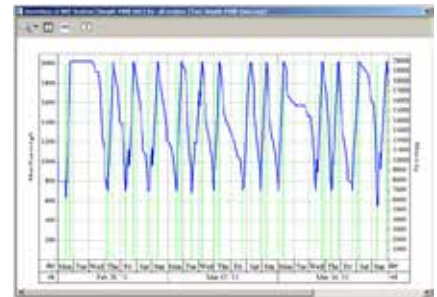
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Magnus Schroeder from Just Evotec Biologics presented their advanced integrated, flexible JPOD facility that is conducive to BCM. In their facility design, post-viral filtration operations are segregated from pre-viral filtration. The JPOD facility is a series of modular class B and C rooms in a class D “ballroom.” The modular design makes the facility very flexible, and it is currently scaled for a 1,000-L-scale single-use bioreactor for a BCM process.

## A STATE OF CONTROL

In any manufacturing process, control is essential. Control means knowing what is happening and monitoring critical process parameters (CPPs) while making changes as needed. Input and output for the process must be controlled, and a state of control must be maintained throughout the process. Understanding what is occurring at all times and being able to assess the quality of the product are essential to developing a successful process. This allows the process to progress smoothly from one step to the next and to be able to determine when a deviation occurs, which might require diverting and sequestering the product stream until the deviation is resolved.

Not surprisingly, BCM processes can be quite complex to control, requiring the monitoring of numerous parameters throughout the process, from the upstream production steps to the downstream purification steps. The BCM processes discussed during the workshop used various inline analytics for monitoring certain conditions and integrated control modules to maintain control over their process. In the upstream production steps, control and monitoring can include the conditions in the perfusion reactor like temperature, pH, and dissolved oxygen [4]. At the same time, in the downstream purification portion, CPPs may be monitored using various technologies [12]. Aseptically taking samples from the production stream can be helpful in maintaining control of the process.

Jens Poschet of MilliporeSigma presented their MAST automated aseptic sampling system, which can be integrated into various steps of the BCM process to allow for automated sample acquisition. These samples, taken from both upstream and downstream operations, can then be diverted to various at-line or offline instruments without disrupting the process stream.

Daniel Some from Wyatt Technology presented their ultra-DAWN real-time light-scattering instrument for inline monitoring and real-time release of product. This multiangle light-scattering instrument measures high molecular weight species and particle counts in solutions with changing protein concentrations. The work presented was part of the BioPhorum real-time release workshop [13].

Automated process control systems, like Delta V, are often employed to control the various aspects of a continuous process. In Merck’s process, this involves 80 to 100 parameters, and higher titers of product coming out of the bioreactor automatically lead to faster flow rates for the process. The goal is to achieve a steady state in the upstream process before loading the downstream process.

Pall also discussed the titer variations they observe in the perfusion bioreactor, which can be challenging for controlling the downstream purification process. They use remote input/output modules to monitor process parameters like concentration and aggregate removal. This automated control allows for responses like diverting the product stream to a waste tank in response to a failed pH probe, slowing a pump speed in response to a pump flow mismatch, or automatic diversion to an alternative filter unit in response to filter fouling, all without human intervention. Evotec Biologics also reinforced the consensus in the industry that it is automation that enables the success of their modular facility for BCM.

Being able to fully understand a BCM process and how various aspects and variations in the process affect the product outcome can be achieved using a digital twin, which is a digital representation or simulation of the real-world process. Rui Wheaton and Ahsan Munir from National Resilience, Inc. presented their digital twin of an integrated BCM process. This digital twin involves real-time process modeling and data analytics based on a feedback loop of process control. The use of a digital twin allows for analysis of how changes to one part of the process, like an unplanned deviation, affect the other parts of the process. This allows for derisking of many aspects of the process, but, as with any model, it needs to be validated against a real-world process. AstraZeneca also uses data analytics, machine learning, and artificial intelligence to better understand and control their BCM system.

## REGULATORY RISK

As discussed previously, the advantages of continuous processes to produce biologics are numerous. But, as with any novel technology, there are risks in adopting the technology. Regulatory risk can be broken out into two parts: uncertainty of what needs to be included in the filing, and comparability risks if the BCM technology is being implemented postapproval or late in the development life cycle.

The Emerging Technology Program (ETP) from the FDA is a collaborative program where industry representatives can meet with the team at the FDA to discuss novel technologies prior to filing regulatory submissions. Joel Welch from the FDA presented an overview of the ETP and opportunities for collaborative interactions. Early collaboration on any new technology is key to the success of the program, and the FDA encourages sponsors to reach out to the ETP early in their development process.

Interactions between the sponsor and the FDA may include knowledge transfer and site visits to better understand the technology. These early engagements ensure that the FDA reviewers and industry are ready for future regulatory filings that include these new technologies and can lead to predictability of review. Once a technology graduates from the ETP, it is no longer considered emerging, and it can proceed fully through standard assessment. As of August 2022, 46 continuous manufacturing technologies had been accepted by the FDA into the ETP.

## ADOPTION OF BCM

Genzyme was an early adopter of BCM technologies [14], and when Sanofi acquired Genzyme in 2011, the development of BCM continued. Nate Ostberg from Sanofi discussed how a perfusion process can rapidly deliver complex protein drug substances to cut the time to first-in-human trials and cycle times, with as little as 35 weeks between the first transfection of cells and drug substance availability for toxicology studies. Sanofi is developing a platform process that they plan to use for late-stage commercial processes. They use a scale-down model for process development, but one of the advantages of their platform is that pilot and GMP manufacturing can be performed at the same scale.

Sanofi also found that they can often take a cell line and move it from a fed-batch to a perfusion bioreactor with little adaptation required. They have developed continuous capture for two biologics produced by an updated perfusion process. One of the keys to adopting BCM was to demonstrate sufficient comparability to avoid additional clinical trials for licensed products. Sanofi's single-use BCM line, which was smaller and less expensive to build than a fixed facility, is being examined for processes for various molecules, including mAbs and enzyme replacement therapies, in an existing facility.

Merck also plans to use the same scale BCM process for development, clinical, and commercial runs. This has several advantages over fixed facility manufacturing. The formal process characterization execution for all unit operations of a fixed process can last nine months. For example, the ultrafiltration/diafiltration (UF/DF) application for a traditional scale-down experiment requires larger amounts of material per run and can only conduct one experiment at a time, which makes this process-intensive for materials, time, and personnel. This poses a challenge for resources, as many experiments are needed for a typical UF/DF study. This hurdle can be overcome by using high-throughput systems, which enable parallel experimentation requiring only a fraction of the resources.

Rob O'Keefe from Eli Lilly and Company discussed their manufacturing and facility strategies with regards to next-generation bioprocessing. There is concern within Eli Lilly that conventional stainless steel facilities for production of mAbs may be getting too large and BCM may offer an attractive alternative. Eli Lilly compared stainless steel with hybrid and BCM facilities using a 6,000-L disposable bioreactor, including a strategy where two bioreactors feed into one downstream process.

They looked at the economic benefit and cost of goods for the various facilities. Hybrid and continuous facilities in the 1,000 to 5,000 kg per year range are a better option economically than stainless steel facilities. Once production surpasses 5,000 kg per year, however, the cost per gram and the net present costs begin to converge. It is important to focus on the cost of goods for any future gains to break the convergence above 5,000 kg. The projection is that regardless of the optimization effort, there is probably a ceiling of \$20–\$30 US per gram. The key takeaway is that BCM leads the way in all the metrics.

As previously established [2], water is the single greatest contributor to a biologic product process mass intensity (PMI). Due to the lack of clean-in-place and sterilize-in-place requirements, Eli Lilly demonstrated that BCM processes featuring single-use equipment significantly reduce water use. Because BCM processes can be fully contained, the energy consumption can be reduced by lowering the required room classifications.

In agreement with Eli Lilly's finding regarding PMI, AstraZeneca reported a 5-fold reduction in PMI for a BCM process compared to a noncontinuous batch process. They also showed that a commercial facility for batch manufacturing can cost \$700 million US and take five to six years to build, whereas an equivalent BCM facility using single-use equipment is one-third the size, costs 40% less, and can be built in half the time.

Transcenta Therapeutics Inc. is developing a platform process to support internal drug development as well as contract development and manufacturing organization (CDMO) services. Chris Hwang explained that pricing pressures, especially in developing countries like China, combined with demand uncertainty and the need for rapid response, are driving the development of their single-use hybrid BCM platform and modular facility design. They demonstrated that their "plug and play" continuous perfusion platform can increase cell culture process output by more than 8-fold when compared to same cell lines in fed-batch mode, whereas their "push to high" platform can push productivity even further.

Transcenta reinforced the importance of the cell culture process being under a state of control and integrating with intensified and automated downstream using BCM to debottleneck the upstream production. Rather than end-to-end continuous downstream, they elected to develop and implement hybrid continuous downstream processing, in partnership with MilliporeSigma, given the small footprint of its multiproduct single-use facility and the need to minimize complexity and risks for their GMP implementation in 2023. Overall, they demonstrated by implementing BCM in a small, nimble, and low-cost single-use facility can achieve the output of larger, more costly, and slower to build facilities while driving cost of goods down.

Cost of goods is also driving Parvus Therapeutics, Inc. to explore BCM to produce their Navacims [15], which target cells that cause autoimmune disease and convert T-reg cells into suppressor cells. Joel Bruegger explained how Parvus uses a perfusion process to produce the protein component of their therapy and to recycle unconjugated proteins to increase the efficiency of their nanoparticle formation during conjugation. They get better titers with a perfusion bioreactor and better conjugation efficiency by recycling, which will drive down the cost of goods for their product.

## CONCLUSION


The workshop was well-received, the presentations were enlightening, and the panel discussions following each session were robust. There is momentum within the biologic manufacturing

world to move toward BCM. This effort is being driven by many large pharmaceutical companies like Sanofi, Eli Lilly, Merck, and AstraZeneca who attended the workshop. This migration is also being supported by contract organizations and vendors that are innovating in this space.

Companies like Fujifilm Diosynth, Just Evotec Biologics, Transcenta, and National Resilience are all developing processes and technologies to support BCM, and equipment innovators like Pall, AK Bio, Wyatt, and MilliporeSigma are providing novel solutions to overcome some of the technical barriers for adopting BCM. Further supporting this are programs within the FDA, like the ETP and other recently released guidances, including ICH Q13 and FDA Q13 [16, 17], to help with regulatory uncertainties.

Although many important barriers related to BCM were discussed during the workshop, some areas and topics were underrepresented. Process analytical technologies [12], including inline and at-line analytics, are supporting technologies for maintaining control of a BCM process and an active area of development at USP. Knowing what is happening in terms of CPPs and critical quality attributes of the product in real time or near real time will be helpful as BCM matures toward commercial use. Wyatt and MilliporeSigma presented their novel offerings in this area. Other development is ongoing in this area and could be featured in future iterations of the workshop.

Another important consideration not fully addressed is the durability of BCM processes and equipment. Many BCM processes under development anticipate the use of single-use equipment in at least some of the process steps [18], but even for processes using durable equipment, the question remains, how long can a process be continuously run and still maintain quality? What is the durability of various single-use components, and where are the critical failure points? For example, Merck is using matrix experiments to determine filter lifetimes to failure. How long can a process be run before microbial contamination becomes a risk? During the workshop, Sanofi reported running their process for two months, whereas Merck ran their process for 24 days, with days 14–24 being under steady state. As BCM matures and moves toward general use, questions regarding the durability of the equipment and processes will likely be an important area of investigation.

The organizing committee anticipates that there will be future iterations of this workshop. As the technology continues to mature, the subject areas of the workshop will expand to include these new areas. USP continues to explore the type of tools and solutions to enable the adoption of BCM, and this work aligns well with existing work at USP on pharmaceutical continuous manufacturing including the opening of a new advanced technology lab in Richmond, Virginia [19]. 

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## About the author

**John F. Kokai-Kun, PhD**, is Director, External Scientific Collaboration-Global Biologics for the United States Pharmacopeia. He received his PhD in microbiology from the University of Pittsburgh School of Medicine and has more than 20 years of experience in drug development. He has held various positions with biotechnology and pharmaceutical companies, where his research and development efforts have focused primarily on biologics and vaccines. John was also an Adjunct Assistant Professor of microbiology and immunology at the Uniformed Services University of the Health Sciences and is retired from the United States Army.



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## HEATHER WATSON

Heather Watson has been a member of ISPE for 22 years. She is Chair of the GAMP® Global Steering Committee and has been a recipient of the ISPE Committee of the Year Award on three occasions, and was Co-Chair of the *ISPE GAMP® 5 (Second Edition)* and *ISPE GAMP® Good Practice Guide: Enabling Innovation – Critical Thinking, Agile, IT Service Management* guide teams. She has been the Co-Chair of tracks at several ISPE Europe Annual Conferences and has presented at ISPE annual meetings. As Company Director of TenTenTen Consulting Ltd., she provides support to overcome the business and regulatory challenges to patient safety, product quality, and data integrity within the life sciences industry. A member of the International Coaching Federation, she also offers coaching sessions and mentoring.

GlaxoSmithKline (GSK) was a constant in Heather Watson's life. "I grew up in a suburb of West London, and Glaxo was the largest company in the area. As a child, I always wanted to work there, even though I didn't really know what they did. Ultimately, I was drawn to the pharma industry not as a scientist but in IT as discovering and understanding how computers could help make medicine safer, more readily available, and more cost effective really interested me."

During her 34 years with GSK, Heather changed roles almost every three years, each time with increasing responsibility, before reaching her final role in the company as Director of Computer Systems Quality Assurance, where she implemented strategy, policy, and objectives; identified potential computer compliance risks; and was responsible for delivering departmental programs covering internal computer system audits, external supplier audits, project support, inspection readiness, communication, and education.

Although Heather worked on multiple projects at several sites in many different cities and countries around the world at GSK, one

project stands out among the rest: "Twenty-plus years ago, as part of the Global IT Risk Management team, we identified risks to the company and the pharma industry and had predicted that there would be a pandemic one day. I was very involved with identifying how it would start, how it would affect everyone, and what plans we should put in place. I was in America on business in February 2020. I arrived on Friday evening and on Saturday morning I received a phone call from the GSK travel group saying, 'You're going home now.' I thought, 'Okay, we've gone pandemic because our plan said one of the first things we would do would be to repatriate any staff who were not in their home countries.' From that point on, things rolled out much as we'd predicted and the plan that we'd developed became reality, as COVID-19 took ahold of the world."

As for predictions for the future of computer system validation in the pharmaceutical industry, Heather says that members of GAMP® are always looking at the impact of new technologies and regulations: "Technology like blockchain, artificial intelligence, and machine learning may be new to the pharma industry but not to other industries. GAMP® will be looking at the impact of these and seeing if they have any effects on computer system validation. Once the FDA's computer software assurance guidance is issued, we will review it and understand if there's any impact that we weren't aware of. Because of ISPE, the GAMP® community is able to review and comment on new regulations and that is a great benefit."

Heather says that ISPE's Engage forums are also an excellent benefit to members: "ISPE has so many subject matter experts as members. You can send a question to a whole load of GAMPers and it's rare that somebody doesn't know the answer. It's really interesting because people ask some very simple questions and very complicated ones. But no matter the question, the network is a huge benefit because you will get a good response."

—*Marcy Sanford, ISPE Publications Coordinator*



# CHRISTIAN WÖLBELING

Christian Wölbelling has been a member of ISPE for 25 years. A founding member and current

Chair of ISPE's Pharma 4.0™ Community of Practice (CoP) Steering Committee, Christian has also been very involved with the GAMP® and Process Analytical Technology CoPs, as well as the ISPE Germany/Austria/Switzerland (D/A/CH) Affiliate.

He has been on planning committees for ISPE conferences, on author teams for the *ISPE GAMP® Guide: Records and Data Integrity* and the *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)*, and co-led the *ISPE APQ Guide: Process Performance and Product Quality Monitoring System* author team. He is currently co-leading the team working on an ISPE guidance document addressing Pharma 4.0™. Christian has been with Körber for more than 30 years and is currently Executive Industry Advisor and Senior Strategic Account Manager, based in Lüneburg, Germany.

A digital pioneer for the pharmaceutical industry, Christian began working at Werum Software & Systems (now Körber) in 1992. "Back then, we were a very small company of 65 people. Two of our main clients were makers of airbags and cigarettes — very different products, but similar in that you must be very precise when manufacturing both. We developed recipe management and manufacturing software which controlled and documented these processes."

"After the reunification of Germany, many pharmaceutical companies were being built. At Werum, we started developing software for Jenapharm, which is now a part of Bayer, and a generics company in Slovenia. These initiatives grew to projects with Novartis, Organon, Novo Nordisk, AstraZeneca, Boehringer Ingelheim, Bayer, Amgen, Merck, J&J, and many other top pharma manufacturers."

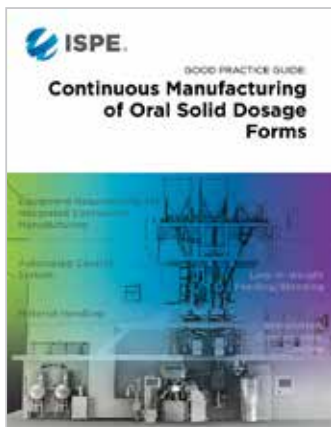
Now Körber is an international technology group with about 12,000 employees and more than 100 locations worldwide. The Körber Business Area Pharma offers a unique portfolio of integrated solutions along the entire pharmaceutical value chain.

An expert in automation and process optimization, Christian and fellow ISPE member Marcel Staudt originated the concept of Pharma 4.0™ in 2015 as a "plug and produce" concept to bridge the automation concepts found in Industry 4.0 with the pharmaceutical ICH guidelines. Open to all ISPE members, the Pharma 4.0™ CoP's objective is to help pharmaceutical organizations leverage the full potential of digitalization to provide faster therapeutic innovations and improved production processes for the benefit of patients. Subcommittees within the CoP are working on holistic digital solutions, process maps, critical thinking, Validation 4.0, machine learning and automation, continuous process verification, and process automation.

Christian believes, "If we break the silos between quality, operations, and engineering, and allow them to work together, we can make this data-driven holistic control strategy happen. Also, we have to digitalize the Pharma Quality System as of ICH Q10. This is what the Pharma 4.0™ operating model is, one of its focus areas. It is bringing the regulatory piece together with the digitalized operations and best-practice engineering pieces."

—*Marcy Sanford, ISPE Publications Coordinator*

# A Comprehensive Reference for Continuous Manufacturing of OSD



The pharmaceutical industry began applying the principles of continuous processing to the manufacture of oral solid dosage (OSD) forms in the mid-2000s. The consensus among experienced practitioners is that the continuous approach has numerous benefits. “Continuous manufacturing provides for a full range of product life cycle, from small volume clinical production to large volume commercial production, with minimization or elimination of scale up activities, all leading to Real Time Release. It offers potential safety benefits and requires a smaller facility footprint,” said Guide Co-lead Dave DiProspero, Director of Pharmaceutical Process Technology, CRB.

## NEWLY RELEASED

### ISPE Drug Shortages Prevention Model: Guidance for Drug Shortage Prevention Excellence



The 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 Task 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.

ISPE Members can download a complimentary copy at [ISPE.org/DSPM](https://ISPE.org/DSPM)



However, there are still many challenges to widespread adoption. The ISPE OSD Community of Practice formed a working team in 2017 to advance the use of continuous manufacturing in the pharmaceutical industry and to increase the long-term efficiency and affordability of the manufacture of OSD products. The team, composed of end user pharmaceutical companies, equipment vendors, and academics, set out to establish equipment requirements, identify opportunities for harmonization and flexible integration, and suggest enhancements to current equipment. The collective output forms the basis for the *ISPE Good Practice Guide: Continuous Manufacturing of Oral Solid Dosage Forms*.

The consensus among experienced practitioners is that the continuous approach has numerous benefits.

“This guide is intended to serve as a comprehensive reference for continuous manufacturing of oral solid dosage forms, providing guidance for pharmaceutical companies, regulators, engineering firms, and vendors engaged in this emerging technology,” said Guide Co-lead Gregory Connelly, Senior Director, Continuous Manufacturing, Vertex Pharmaceuticals.

For more information about the guide, visit [ISPE.org/publications/guidance-documents](https://ISPE.org/publications/guidance-documents)

—Marcy Sanford, ISPE Publications Coordinator



# ISPE UK Emerging Leaders Awards

By Zam Shabeer Thahir, CEng, MEng, Cantab

The UK Emerging Leaders Awards program is an exciting initiative for ISPE because it recognizes and celebrates the efforts and contributions of young engineers in the UK pharmaceutical engineering and manufacturing sectors.

Globally, the ISPE UK Affiliate is the only ISPE affiliate to have a dedicated awards program for the Emerging Leaders.

## CREATING THE AWARD

The awards were created in 2021 by Zam Thahir and Craig Milner, both active members of the ISPE UK Affiliate. According to Thahir, ISPE UK Emerging Leaders Chair, “we identified a gap in the awards program. Because only long-serving members of ISPE UK have traditionally won the awards at the ISPE UK annual awards dinner, any student or recent graduate had minimal chances of winning. Hence, we set up the Emerging Leaders Awards, where anyone working in the UK and under the age of 30 are eligible to apply.”

## SUPPORTING THE NEXT GENERATION

The awards have been a tremendous success and have received glowing feedback in terms of promoting our industry and encouraging the next generation of pharmaceutical engineers and leaders. The ISPE UK Affiliate hopes that this initiative drives the younger demographic to become interested in pharma and in ISPE, and benefit from a rewarding career in life sciences and the vast benefits an ISPE membership offers.

## EU HACKATHON

“The most exciting part of winning the awards are, of course, the prizes,” said Thahir. “And the most popular of the prizes is the fully sponsored trip to the ISPE EU Hackathon held in conjunction with the ISPE Europe Annual Conference.” The EU Hackathon is a weekend-long competition for students and recent grads at the ISPE Europe Annual Conference. Since the Hackathon’s inaugural year in 2021, the ISPE UK Affiliate has sponsored the winners at future events, including the 2022 ISPE EU Hackathon in Madrid and the 2023 ISPE EU Hackathon in Amsterdam.

The 2024 ISPE EU Hackathon will be in Lisbon, and we encourage students and recent grads to apply for the awards. We are also reaching out to managers, mentors, and senior members of the



Zam Thahir, ISPE UK EL Chair, Jodie Winder, winner of a 2021 UK EL Award, and Thomas Hartman, CEO and President, ISPE.



Zainab Aslam, winner of a 2022 UK EL Award and Mike Potts, Senior General Manager, Thermo Fisher Scientific, sponsor of the awards.

industry to encourage their padawans to apply for the award or to make them aware of the awards program. A special student category is also available for those in higher education, internships, and apprenticeships. The application window opens in summer 2023 and will be advertised on the ISPE UK Emerging Leaders LinkedIn page.

## SPONSOR

The awards have been made possible due to the generous support of our sponsor, Thermo Fisher Scientific, Swindon, UK. The ISPE UK Affiliate and Emerging Leaders are grateful to Mike Potts, Senior Director and General Manager, Thermo Fisher Scientific, for his continued support in sponsoring the awards.

## OTHER WAYS TO CONNECT

In addition to the awards, the ISPE UK Emerging Leaders organizes several other events to inspire, connect, and educate the

emerging leaders. We have set up a Student Chapter at the University of Leeds and are currently setting up a student chapter at the University of Sheffield. The Student Chapters are a great opportunity to be connected to the industry and to develop one's professional network at a very early stage in one's career.

If you are a student, education staff member, recent grad, or apprentice interested in participating or joining the committee, please get in touch with us at [emergingleaders@ispeuk.org](mailto:emergingleaders@ispeuk.org). We

are open to ideas to provide further value to our members and always welcome volunteers for this cause.

### About the author

**Zam Shabeer Thahir, CEng, MEng, Cantab**, is Chair of the ISPE UK Emerging Leaders. He is a Chartered Senior Process Engineer at IPS—Integrated Project Services, responsible for critical/clean utilities. Zam is of Sri Lankan origin and holds a master's degree in chemical engineering from the University of Cambridge. He has been an ISPE member since 2015.



## Meet the ISPE STAFF



EDYNA MIGUEZ

In each issue of *Pharmaceutical Engineering*®, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Edyna Miguez, Membership Growth Manager.

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

As Membership Growth Manager, I communicate the opportunities and benefits available through an ISPE membership to active and prospective members. This often includes collaboration with Affiliate and Chapter leaders and passionate members, which is one of the best parts of my job. I take great pride in helping our members make the most of their experience by leveraging the ISPE network and resources to advance their careers and make their mark on the industry.

I also work as Program Manager for Women in Pharma®. This quickly turned into both a passion project and a large part of my daily responsibilities. I feel so fortunate to be able to work on it so closely.

Through Women in Pharma programming, I get to collaborate with incredible pharma professionals across the globe, all of whom are working to create a more equitable pharmaceutical industry. I've seen the program mature in such a short amount of time thanks to the commitment of our volunteers and International Steering Committee. I'm excited to continue watching it flourish and make an impact as it applies to diversifying the industry and making the world a more inclusive place.

### What do you love about your job?

I love the international component of what we do. I really enjoy meeting members from

different parts of the world, learning from their experiences, and gaining new perspectives. Through our many conversations, both in person and online, I've gained a better understanding of the various cultures that make up the ISPE member base.

Our members are inspiring, and the work they are doing is incredible, especially when they share their motivations. When you realize how much they believe in the work they are doing, and how improved patient lives and quality of life are their driving force, you can't help but be truly inspired. I absolutely love knowing that I can help them on their journey in the smallest way as they continue to save the world. It allows me to feel like I'm a part of something much larger than myself, and that I'm making a real impact.

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

When I'm not at work, I am spending time with my little family. My husband and I have a three-year-old son and two dogs. We love to travel with our son, which at this stage includes plenty of trips to Disney World. We try to visit at least one new city a year, and we try to escape a few times a year for long weekends and resets. When we're not traveling, we remain very activity-driven; we spend our weekends at the zoo or local science museum, hoping to nurture our son's natural curiosity for the natural world and anything science. We are lucky to live close to family and old friends, and so we spend a lot of time at family gatherings. We love to try new foods and are constantly discovering new restaurants, and I love to indulge in pop culture (anything Bravo, please!).



# Make Connections that *Matter*

ISPE highlights talents and contributions of global pharmaceutical industry members through in person and virtual engagement opportunities. Members connect on career advancement topics, and develop meaningful connections with industry thought leaders and the emerging workforce, creating opportunity for thought exchange, innovation, and collaboration.

**42 YEARS** of serving pharmaceutical professionals and leading innovation to improve patient health

**22,000+ MEMBERS** in over 120 countries

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**A ROBUST LIBRARY** of on-demand training and e-learning resources and copies of the award-winning publication: *Pharmaceutical Engineering*<sup>®</sup> Magazine

**70+ GUIDANCE DOCUMENTS**, including over 35+ translated into languages other than English and 20+ complimentary ISPE Good Practice Guides\* that address industry best practices and regulatory expectations

**SIX INTERNATIONAL CONFERENCES** and hundreds of digital engagements and training courses per year

**24-HOUR ACCESS** to topic-specific Communities of Practice comprised of ISPE members worldwide

\*GAMP\* Good Practice Guides are excluded from this member benefit.



[ISPE.org/Renew](https://www.ispe.org/renew)



# ChatGPT, BARD, and Other Large Language Models Meet Regulated Pharma

By Frederick Blumenthal, Martin Heitmann, Stefan Münch, and Brandi Stockton

ChatGPT and other large language models are positioned to change the world. They can also shift acceptance and prevalence of machine learning solutions in regulated industries in general. However, their arrival requires reconsiderations on risks, quality assurance, and validation from a GxP perspective.

ChatGPT [1] has taken the use of artificial intelligence (AI) to the next level, reaching a global user base beyond the established AI circles, and other large language models (LLMs) like LaMDA as in Bard [2] followed. But can we imagine applying a tool like ChatGPT in a safety-critical, product-related environment? To this end, we need to understand what ChatGPT is: As an LLM within the space of generative AI, it can create content, and therefore contrasts other objectives of machine learning (ML) to generate point estimate predictions or suggestions on categories or classifications. That said, is this technology also helpful in regulated areas of pharma? We will examine this question from quality, risk, and efficiency perspectives and discuss how such tools can shift the way we think about validation and quality assurance.

ChatGPT is commonly used to refer to the chatbot web interface, and the underlying model. For the sake of readability, we will use it interchangeably for both interpretations throughout the article.

In sections where we applied ChatGPT for example cases, we indicate this as such:

- The question or remark from us is labeled as **Authors**.
- The response by ChatGPT is marked as **ChatGPT**.
- All respective content is enclosed in quotation marks.

For these ChatGPT examples, we use the web interface of ChatGPT: <https://chat.openai.com/chat> (recorded 9 February 2023).

**Authors:** “Is ChatGPT also useful for the use in regulated areas of pharma?”

**ChatGPT:** “Yes, ChatGPT can be useful in regulated areas of the pharmaceutical industry, such as providing information on drug products, their uses, dosages, side effects, and interactions with other medications. However, it’s important to note that ChatGPT is a general language model, and its output should not be considered medical advice. In regulated areas, information should always be validated and verified by a qualified healthcare professional before being used in patient care or treatment decisions. Additionally, the use of AI in regulated areas is subject to specific laws, regulations, and guidelines, and it’s important to ensure that any use complies with these requirements.”

We note the following about this response. First, ChatGPT does not claim that it is useful: it just states that it *can* be useful. We share this view and will elaborate on that with respect to governance and quality assurance.

Second, ChatGPT provides a very broad, high-level overview of possible activities and tasks for which it may be used in the pharmaceutical industry. However, it does not provide further information on how it could be applied. Also, we think that ChatGPT can offer further use cases that are of equal importance in our view.

Third, we note that ChatGPT, as it mentions in its own response, is a general language model and accordingly uses terms such as “qualified healthcare professionals” and “medical advice.” Specific aspects of pharmaceutical roles (e.g., quality assurance) are not mentioned here. We do acknowledge that ChatGPT points out that its answers should be verified by qualified healthcare personnel.

In summary, ChatGPT offers an interesting starting point to think about the use of such systems or other, tailored, generative AI systems in regulated areas. But, as we see in this first example, this can only be the start of critical thinking and careful evaluation of information.

We structure the rest of our article as follows: We provide an overview of how LLMs operate and how ChatGPT was constructed, describe use cases of ChatGPT as an example of generative AI that is optimized for chatting, and present use cases

ranging from the original idea of chatting and text creation to software development. Next, we discuss the risks related to the use of ChatGPT and LLMs in general. We transfer the capabilities of ChatGPT to specific use in context to the pharmaceutical value chain, and elaborate on the context of use in the regulated areas of pharma, considering ChatGPT and LLMs in general. Our article concludes with an outlook on how the use of LLMs may evolve, beyond the current hype.

## OVERVIEW OF LLMs AND TRAINING OF LLMs

Simply put, a language model is a probability distribution over sequences of words, i.e., when given a text sequence, the model can predict what likely comes next. The term *large language model* is not clearly defined but usually refers to language models that are based on very large neural networks. By training to predict the next word, LLMs learn the underlying patterns and structure of the language as well as facts about the word. These models can subsequently be applied to a broad range of language processing and language understanding tasks.

Although the first neural language model was proposed over 20 years ago [3], there are some key innovations that led to the impressive capabilities of modern LLMs, in particular:

- **Hardware advancements:** The availability of specialized chips like graphics processing units (GPUs) and tensor processing unit (TPUs), which allow for faster processing of large data
- **Software advancements:** New neural network architectures, like transformer models that are more efficient for processing sequences of text, and more advanced numerical optimization techniques
- **Larger and more diverse training datasets:** Modern LLMs are trained on much larger and more diverse datasets than older models

For example, GPT-3 [4], considered one of the most powerful language models and what ChatGPT is based on, is a large transformer model with 175 billion parameters that was trained on about 45 terabytes (hundreds of billions of words) of multilingual text data (crawled websites, books, and Wikipedia).

The training of such language models is often referred to as pre-training because the pre-trained language model was usually tailored to the desired task on a supervised (labeled) dataset to perform a specific task: for example, sentiment classification or extraction of certain entities. The resource-expensive pre-training (which only has to be done once) gives the model the general linguistic capabilities, whereas the tailoring adapts the model parameters to the specific task. This approach is still reflected in the name GPT, which stands for Generative Pre-trained Transformer.

LLMs such as GPT-3 can be applied to natural language processing (NLP) tasks without further tailoring by only providing the input text to model together with an appropriately formulated prompt (i.e., a natural language instruction describing the task). This so-called zero-shot approach has the strong advantage that no data must be labeled for the tailoring step and that the same

model can be used for many different NLP applications. However, this approach usually does not reach the model performance of tailored models. Putting a few input-output examples in front of the actual prompt often leads to significantly better results. This approach is called few-shot learning.

Thus, LLMs such as GPT-3 can be used to perform NLP tasks. However, these models, which are merely trained to predict the statistically most probable next word, are often not very good at following instructions and sometimes generate untruthful and toxic outputs. ChatGPT is a tailored derivative from GPT-3 to align the LLM better with the users' intentions, i.e., to generate responses that are more helpful and safer and to interact in a conversational way [5].

To this end, the model is provided with examples of text inputs and respective outputs written by human labelers. In addition, a relatively new approach around LLM called reinforcement learning with human feedback (RLHF) has been used to train the model, which optimizes the model based on outputs that have been ranked by human labelers. Ranking is a much easier task and much more efficient than writing outputs. As an extra layer of protection against undesired outputs, ChatGPT uses an algorithm to classify and filter out harmful content.

During the last few years, various LLMs have been developed by big tech companies, AI startups, and research initiatives. The most popular model is arguably the GPT-3 model family from OpenAI, a closed model that is commercially available via application programming interface (API) for inference and fine-tuning. The popular PaLM model by Google reportedly has very strong capabilities, but this closed model is not publicly available. Other popular models are OPT by Meta (an open model with use-based restrictions, e.g., noncommercial use only) and BLOOM by the research initiative BigScience (an open model with small use-based restrictions). It can be expected that many new foundational LLMs as well as specialized models (such as dialogue systems) will be developed soon.

Given this overview on how ChatGPT is constructed and trained, we will elaborate on specific quality and control implications for application in regulated areas in our article.

## USING ChatGPT

Through our use of ChatGPT as one representative of LLM applications focused on chat tasks, we identified the following use cases:

- **Brainstorming assistant:** ChatGPT can provide further points for consideration and refine a suggestion based on an idea.
- **Writing assistant:** Provided an idea of content to be produced, ChatGPT can create a complete paragraph, adding details and further information. It can also tune the text to a specific audience or style.
- **Fine-tuning assistant:** Many language contributions in the pharmaceutical industry such as articles, evaluations, and reports are inherently complex due to the business content. However, complex grammar presented in these publications is often unnecessary. ChatGPT can be used to simplify the language, either as author or in the position of the audience.

- Knowledge base search: A topic can be explored and described in various tones from simple understanding to deeper and expert information. The chat nature of ChatGPT allows us to refine the insights gained and balance critical questions and exploration, as shown in the introductory example.
- Software engineering: ChatGPT can provide full implementations, including syntax, given a description of the intended use. It also can provide automated tests to verify the implementation.
- Proofing and robustification of software: ChatGPT can detect errors in implementation and provide hints on how to resolve them in the code.

### Case 1: Creating Paragraphs from a Set of Keywords

**Authors:** “Please provide a section about data integrity in computerized systems from a pharma quality assurance perspective in 100 words.”

**ChatGPT:** “Data integrity in computerized systems is critical for ensuring the quality and safety of pharmaceutical products. From a pharma quality assurance perspective, data integrity refers to the accuracy, consistency, and reliability of electronic data used in pharmaceutical operations. This includes data generated from laboratory equipment, manufacturing processes, and business systems. Quality assurance must ensure that data is protected from unauthorized changes and accurately reflects the intended state. This can be achieved through implementing effective controls, such as secure systems, data backup procedures, and access controls. Additionally, regular audits and inspections should be conducted to verify the accuracy of data and identify any discrepancies. Ensuring data integrity is essential to meet regulatory requirements and maintain the trust of patients and stakeholders.”

**Authors:** “Please provide a section about data integrity in computerized systems from a software development perspective in 100 words.”

**ChatGPT:** “In a pharmaceutical software engineering context, data integrity refers to the accuracy, consistency, and reliability of data stored in computerized systems. This is a crucial aspect of pharmaceutical software as it directly impacts patient safety. To ensure data integrity, pharmaceutical companies must implement strict validation processes, perform regular backups, and have in place robust security measures to prevent unauthorized access and data manipulation. Additionally, software systems must comply with regulatory standards such as 21 CFR Part 11, which lays down guidelines for the use of electronic records and signatures in the pharmaceutical industry. Maintaining data integrity requires a combination of technical, organizational, and procedural measures to ensure that data is protected at all stages of its lifecycle.”

We evaluate these responses by ChatGPT as follows. Both responses provide an adequate description of data integrity and

its importance, but the responses are incomplete, as they do not cover all aspects of the ALCOA (attributable, legible, contemporaneous, original, and accurate) principles and lack some well-known extensions, such as traceability. None of the responses point to the relation of data integrity, product quality, and patient safety. However, they emphasize the importance of data protection and access control.

As expected, both responses are similar. The small, but subtle, difference in the request is well-reflected in the responses and the differences are obvious at first glance. The second response refers to some aspects of system design. However, crucial elements like a software development life cycle approach to ensure data integrity are not mentioned. Still, the response concentrates on business matters, which may be caused by “remembering” the context of the first request. Thus, it is important to consider that responses vary depending on a chat’s history. Surprisingly, the number of words is greater than 100 in both cases (~120). The clearly formulated nonfunctional requirement is therefore not fulfilled.

### Case 2: Refining Natural Language

**Authors:** “Please simplify the language in the following section of text” (example text is taken from [6]): Once the intention of use, the addresses and the acceptable risks have been identified, the solution should be designed in a way that it is able to fulfill its specific quality expectations. The impact of the steps before on the modeling decision cannot be underestimated: When users are confronted with the solution’s results in every single case to build their decision on the AI output, a different modeling strategy may be pursued in comparison to a situation where the solution operates in a mode when only exceptions are handled by operators. However, it is important to critically reflect the decisions made so far, as more understanding of the use case will be gained once the first models are evaluated. Prototyping strategies for early feedback and alignment reduce the acceptance risks further down the development process stream. In this constructive process, documentation regarding the decisions made are important to justify the model and explainability mechanism selection in an audit context.”

**ChatGPT:** “The solution should be made to meet its desired quality standards. The way it’s made depends on how it will be used and who will use it. The impact of earlier choices can’t be ignored. The solution’s results will be different if users always use it to make decisions compared to if it only helps operators with exceptions. It’s important to keep evaluating the choices made. Testing the solution early helps reduce risks. Keeping track of the decisions made helps explain why certain choices were made in the future.”

We evaluate these responses by ChatGPT as follows. The text is considerably simplified in language. However, the inner logic of the section is not reflected anymore; for instance, “the decisions” are not adequately integrated into the text. ChatGPT does not identify AI as part of the key message. Thus, part of the context is

missing and leads to misunderstanding of the new text. In addition, it seems as if the role of “explain” is turned around; we interpret ChatGPT’s response more in the sense that the process outcomes should explain the decisions made, whereas the original piece elaborated on the explainability of algorithms. However, we acknowledge that we see this paragraph from the authors’ view and it might be difficult for a human to grasp the meaning of this isolated section, taken from a technical article handling a complex topic.

### Case 3: Creating Software or Base Software Kits

**Authors:** “Please provide Java code that is able to run a linear regression on a tabular data set. Can you also provide a test case for your class?”

In response, we received the requested Java code with a short explanation text at the end, not shown here for the purpose of readability, while copies were kept.

We evaluate it as follows. We verified that the code compiles and runs in Java 17. The code is generally readable: common variable names for linear regression are used. The code style conforms to best practices, e.g., using the constructor for the actual estimation algorithm and providing a separate prediction method. The test case is a reasonable example of application of the code, but not tested in the software engineering sense, i.e., verifying the functionality is done by comparing the expected prediction with the actual prediction. In that, the methodological quality of the linear regression is assessed, but not the correctness of the implementation.

## RISKS INHERENT TO THE USE OF LLMs

Although ChatGPT has its capabilities in various areas, as shown previously, it does not come without risks, which we need to consider in all use contexts, but even more so from a risk control perspective in the highly regulated pharmaceutical industry. We identified 10 key risks, which also apply to more general use of LLMs.

### Quality and Correctness

ChatGPT can provide content quickly. However, as we already saw in the examples, the content needs to be reviewed and verified by a subject matter expert. The LLM may invent content (“hallucinate”), so it is the user’s responsibility to decide which parts are of value for the intended use.

### References and Verification

ChatGPT does not offer references per se to verify the information. The chat functionality can be used to elicit references on this topic; however, these “references” may be poor quality or may be fabricated. The LLM may invent titles and authors because it learned typical patterns in references, but it does not know how to verify the integrity of references. This raises concerns about the general traceability and trustworthiness of the generated responses and strengthens our assertion that each response must be carefully verified by a subject matter expert. However, our experience shows

that using the chat feature to request an explanation of the results sometimes reveals interesting background information.

### Reproducibility

Responses by ChatGPT may change; a “regenerate response” option is deliberately provided. Hence, traceability of results and content is limited, and sensitivity to input is quite high, as was shown in previous examples. Retraining and updates of the hyperparameter configuration used for training may include other sources of variation in the responses, as in other applications of ML models, i.e., the model evolves over time.

### Up-to-Date Information

When operating in a frozen mode regarding training data, language models only capture information to a specific time horizon (at the time of writing, training data for ChatGPT covered until about the fourth quarter of 2021 [7]). Information beyond this horizon cannot be known (or only to a limited amount) in a particular version of the model, which might lead to responses that do not reflect the current state of information.

### Intellectual Property and Copyright

In a sense, the whole training data universe can be considered the source of each answer. Therefore, the exact information—or code—might already be created by a third party. Hence, double-checking the intellectual property of the results is important to mitigate legal risks. This also affects the input provided to ChatGPT, which may also fall under intellectual property and copyright considerations.

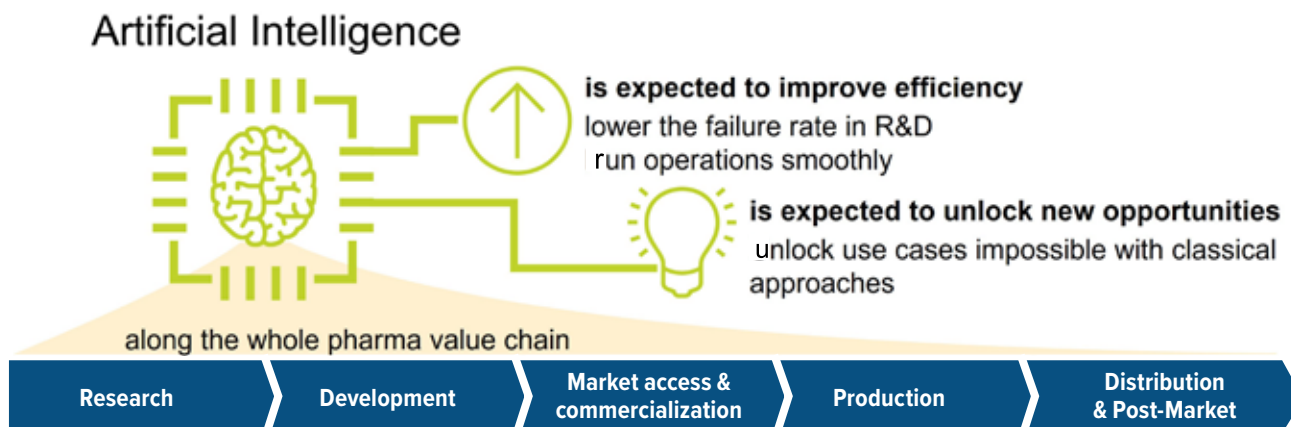
### Bias

Bias may result from various steps in the training steps of ChatGPT: the pre-training on the GPT-3 model, fine-tuning, and moderation. The pre-training was trained on unsupervised data to predict the next word; therefore, the model learns biases from this data set. During the fine-tuning process, operators provided “golden responses” to chat input. Even if done to the standards of OpenAI principles, bias in this human opinion cannot be excluded. Eventually, ChatGPT is moderated to prevent harmful content, which is again trained on labeled data and may carry biases. In summary, the combined effects in this three-step process are not verifiable from the user’s perspective. Therefore, users risk distorting their own content if they leverage ChatGPT’s results without critical thinking.

### Formation of Opinions

Regarding the previous point, particularly in evaluation exercises such as assessments of incidents, ChatGPT may form “an opinion” and hence influence a decision-making process. However, we like to note human decision-making is not bias-free either; thus, ChatGPT may contribute a second perspective on the question at hand, or even multiple perspectives if asked for different angles on a topic.

Figure 1: Application of artificial intelligence across the value chain.



### Service Availability

At the time of this writing, the free version of ChatGPT is not currently stable due to the heavy user load. However, ChatGPT also offers a pro version and API access for use in a professional environment.

### Data Confidentiality

Every input entered into the ChatGPT interface is beyond the control of the users; hence, no internal or confidential information should be transmitted to mitigate legal risks. This limits the use of ChatGPT, especially in the areas of pharma and healthcare, where many use cases involve personalized identifiable information or business-critical information.

### Regulation and Governance

It should be verified if the use of generative AI tools is permitted for the use case by regulatory or internal governance reasons. Due to these risks, some companies already block ChatGPT and similar systems in their network. However, is this the solution? In the next section, we will elaborate on specific use cases, with ChatGPT as a representative of what LLMs can support in the pharmaceutical industry.

## USE CASES OF ChatGPT IN REGULATED AREAS OF PHARMA

Given their general areas of application and risk, where could LLMs like ChatGPT provide value to the pharmaceutical industry, and eventually to patients?

Along the pharmaceutical value chain, we think there are five use cases, discussed next and shown in Figure 1 and Table 1:

1. Research: ChatGPT may be used as a brainstorming assistant to generate ideas on a particular target mechanism.
2. Development: ChatGPT may be used to assist in the writing of study reports, provided case descriptions are given.
3. Market access and commercialization: ChatGPT may be used to

simplify the language of pharmaceutical descriptions to make it more accessible to patients.

4. Production: ChatGPT may be applied to create pieces of software required to control the production process.
5. Distribution and post-market: ChatGPT may be applied to summarize the insights from nonclassical pharmacovigilance sources such as social media.

In Table 1, we present our evaluation of the usage of LLM like ChatGPT in these situations. Based on the use cases, we do not think the use of LLM replaces process understanding and subject matter expertise. Even more, the application of these technologies requires a strong understanding of the use case and the inner mechanics to verify the results provided by the LLM, as well as a sensitivity for further risks arising from the black-box nature of these models.

Therefore, we see the most promising applications in the form of an auxiliary tool. Critical thinking is required to assess the output, regardless of whether this is technical content (code, automated tests) or subject matter content (e.g., created text, reports, or sections). To facilitate critical thinking and maintain quality, standard operating procedures need to define how to use and refine output, as well as to define areas where aid from LLM is ethical and where it is not. One example in which we consider the risk of bias to be critical is around evaluation or assessment, which may affect and shift the views of subject matter experts in the first place.

## WIDER APPLICATION OF LLMs IN REGULATED PHARMA

Do we see the potential of ChatGPT and other language tools for critical tasks as more than an auxiliary tool? In our opinion, it will be difficult to apply an open, public model in a GxP-regulated context for the following reasons:

- The corporation has no direct control of and traceability over the model development process.



**Table 1: Assessment of selected LLM applications along the pharma value chain.**

Case	Potential Benefits	Risks	Assessment
1: Brainstorming assistant for research	Efficiency boost through leveraging already known information  Gain new ideas on mechanisms	Information may be difficult to verify  Lack of references  Depending on the service model chosen, confidential information may be disclosed	Limited use, more in exploratory phases
2: Writing assistant during development	Efficiency boost in creation of study reports  Possible harmonization of style and language in study reports	Misleading summarization of outcomes  Depending on the service model chosen, confidential information may be disclosed	Limited use, only in exploratory phases
3: Fine-tuning assistant for market access and commercialization	Texts with high readability produced  Texts specific to the audience	Possible loss of crucial information and relations	Requires careful review, but may improve on quality of communication
4: Software engineering assistant for pharma production purposes	Efficiency boost with syntactic and semantically correct blueprints or full code  Developers can focus more on functionally valuable tasks  Developers may let the LLM check the code	Incomplete business logic  Errors in implementation  Code that does not comply with usual software design patterns  Copyright violation	High use, both from the developers' perspective and from a quality perspective; confidentiality should be maintained
5: Summarizing assistant for distribution and post-market	Additional input and ideation of structures and patterns	May involve the use of highly sensitive, patient-specific information  Mass of specific input data for a pharma case may be difficult to process by LLM	In our view, this use case can be better handled by other language models that apply clustering techniques over a larger input set

- The corporation lacks control of the horizon of knowledge, i.e., the last point in time from which relevant training data entered the training set.
- The corporation lacks control on labels and feedback that were used for the training process.

However, ChatGPT demonstrated the power of AI in the field of NLP. This means that in a controlled development environment [8], the development of solutions specifically trained for the pharmaceutical or life sciences domain is promising. If such an LLM was integrated into a process controlled by subject matter experts and provided with evidence of improved human–AI–team performance [9] in a validation exercise, these approaches can add value to the process and ultimately to product quality. In terms of the AI maturity model [10], this would refer to a validation level 3 solution.

From a governance and control perspective, risks need to be monitored along the five quality dimensions [11] in the application life cycle, with a primary focus on retraining and refreshing the body of knowledge:

1. Predictive power: Is the output of sufficient quality and is it answering the question asked by the users?
2. Calibration: Does the language model perform sufficiently well within all relevant dimensions of use cases, or does it exhibit critical biases in some use cases?
3. Robustness: Are outputs sufficiently stable over time and are changes in the output comprehensible?
4. Data quality: Are the data used for training and the data provided as input to the system quality assured to best practices of

data governance (e.g., labeling of data, analysis of representativeness of training and production cases)?

5. Use test: Do users understand the link between the problem at hand and the language model's results? Do they adequately react to the language model's output by questioning, verifying, and revisioning the responses?


Even in such controlled situations, we expect that review by a human is required to verify the output in a GxP-critical context. As far as we see, only a subject matter expert can truly evaluate whether a statement in pharma and life sciences in general is true or false.

## CONCLUSION

LLMs and ChatGPT are here to stay. It is on us as users and subject matter experts to learn how to use this technology. This becomes even more important as this technology is more readily available in everyday business applications. In combination with critical thinking, results of these LLMs can also be helpful in the regulated environments of the pharmaceutical industry—not as a stand-alone solution, but as a work tool, boosting the efficiency of various operational units from software engineering to regulatory documentation. Using these services via web interface, business application, API, or commercial cloud services must be seen with the precondition of rigor, quality assurance, and mitigation of legal risks while we may need to be creative in finding suitable use cases.

Additionally, more specialized LLMs are likely to gain traction. As in other safety-critical, GxP-governed areas, these models must be developed under controlled quality and best practice conditions.

This rigor involves the quality assurance of input data, control of the development process and validation, and productive monitoring and quality risk management processes. This again can unlock two new powerful dimensions to true human-AI-team collaboration: boosting efficiency by focusing on the respective strengths of AI and cognitive intelligence with a suitable target operating model.

Therefore, it is paramount that corporations react to these developments by setting adequate standards and controls. In this article, we provided a general overview of potential use cases and risks inherent to the use of such LLMs. Building on this guidance, the application of such models always must be evaluated under the specific intention of use, either in the role of a working aid for subject matter experts, developers, and further staff, or as part of a computerized system itself. 

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# AIR CHANGE RATE REDUCTION DURING OPERATION:

## Success at Roche/Genentech

By Behzad Torabifar, PE and Geoffrey Wing, PE

To improve the energy efficiency of cleanrooms, the Roche Global Engineering and Oceanside facilities and Engineering team collaborated to implement a risk-based approach to achieve lower air changes during operation without adversely impacting the facility, equipment, or reliability, while meeting environmental requirements.

For almost 20 years, it has been known that the original cleanroom ventilation rates from the last century are much higher than necessary to achieve the cleanliness standards set by regulatory agencies. For example, ISO 8 required 20 to 30 air changes in 2001 when Federal Standard 209E was withdrawn. Now most guidance for ISO 8 suggests 10 to 20 air changes per hour (ACH). As such, many of our facilities' engineering groups started to conduct surveys to benchmark ventilation energy use, with the goal to improve the energy efficiency of HVAC systems by reducing air change rates (ACRs).

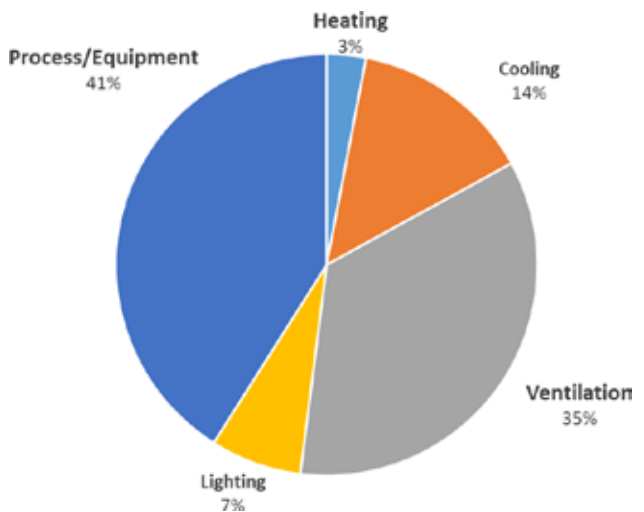
The Roche Global Engineering team developed an Air Change Rate Reductions Best Practices Guide in 2019 [1] to guide these pharmaceutical manufacturing site surveys and to challenge and optimize existing installations that use high ventilation rates with the intent of maintaining particulate levels required for manufacturing environmental quality.

At the time, ISO 14644-16 [2] was not yet released. ISO 14644-16:2019, "Cleanrooms and Associated Controlled Environments — Part 16: Energy Efficiency in Cleanrooms and Separative Devices," provides guidance and recommendations for optimizing energy usage and maintaining energy efficiency in new and existing cleanrooms, clean zones, and separative devices. It provides guidance for the design, construction, commissioning, and operation of cleanrooms.

### COMPANY HISTORY AND SUSTAINABILITY

At Roche/Genentech, our business is focused on the pharmaceutical and medical devices that patients need next. Our ambition lies

Figure 1: Electricity consumption at Genentech California sites.



not only in transforming healthcare through innovative solutions, but also in our contributions to environmental protection. Since 2004, Roche/Genentech has been implementing carbon dioxide reduction measures that have led to a 59% absolute reduction in greenhouse gas (GHG) emissions from our own operations and purchased energy (Scope 1 and 2). In that same period, our revenue has more than doubled [3].

Energy conservation has been a top priority in our GHG emissions reduction strategy. One of the most energy-intensive areas in our pharmaceutical manufacturing sites are cleanrooms, which makes them a great candidate for energy optimization. Cleanroom energy benchmarking studies, in general, show that HVAC energy use in the cleanrooms accounts for 36%–67% of the total facility energy consumption [4]. Although the relative percentages vary due to the energy intensity of the process systems, cleanroom classifications, and the climate, HVAC systems are the dominant contributor to the energy intensity in pharmaceutical manufacturing sites (see Figure 1).

**Figure 2:** Flow chart of phases as presented in Air Change Rate Reductions Best Practices Guide.



**Key:**

ACR: Air Change Rate  
 EMPQ: Environmental Monitoring Performance Qualification

IQ: Installation Qualification  
 NPV: Net Present Value  
 OQ: Operational Qualifications

**MANUFACTURING SITE SURVEY**

The phased approach in the survey requires both an understanding of the requirements and a sequence of progressively more detailed engineering studies to achieve energy-saving potential with minimal wasted effort. The phases of project execution elaborated in Figure 2 are as follows:

- Phase 1: Assess risk and challenge environmental classifications
- Phase 2: Evaluate the opportunity, including numerical evaluation and screening study
- Phase 3: Understand facility performance
- Phase 4: Address findings and implement
- Phase 5: Assure consistency with qualification and ongoing management

**Figure 3:** Oceanside campus.



As shown in Figure 2, implementing ACRs can affect the manufacturing process environment. In most cases, changes that affect manufacturing are done when manufacturing is shut down to minimize the risk to the product. However, when the US Food and Drug Administration (FDA) introduced “Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach” [5] in September 2004, the paradigm shifted and these questions were asked: What is the probability that changing the airflow in a given clean area will affect the process or product in that area? What would be the impact to the process or product in that area if the airflow was changing? This new thinking about the risk of change implementation during production eliminates the need for a shutdown. Now the implementation can focus on risk controls.

**Site Location**

At Roche/Genentech, addressing these questions started in the Genentech facility in Oceanside, California. This facility was chosen because site processing is sealed or can be held in a sealed state for enough time to implement the change in airflow. The goal of this paper is to share that success story of implementing ACR reduction at the Oceanside facility while the cleanrooms were in operation.

Located 35 miles north of San Diego, the Oceanside campus is a multiproduct Chinese hamster ovary (CHO) drug substance manufacturing site with parallel commercial production and launch capabilities that spans 60 acres, with seven buildings and ~575,000 square feet. The facility has 90,000 liters of capacity and is licensed to produce several biological drug substances (see Figure 3). It has 3.5 MW of solar photovoltaic as a combination of ground-mount, carport, and rooftop panels, with a 1 MW, 2 MWh on-site battery energy storage system (installed in 2016), and a 2.5 MW fuel cell (installed in 2019).

Table 1: Air change reduction screening analysis.

Overall Results – cGMP Airflow Reduction Screening Analysis									
Space Type	Number of Rooms	Room Area (ft <sup>2</sup> )	Room Volume (ft <sup>3</sup> )	Baseline AC/Hr	Baseline Airflow (CFM)	Reduced AC/Hr	Reduced Airflow (CFM)	Airflow Savings (CFM)	Energy Cost Savings (\$/yr)
BZ 2	13	3,911	54,681	37.3	38,824	32.4	33,833	4,991	\$22,000
BZ 2A	8	648	5,832	39.1	3,677	36.3	3,475	202	\$1,000
BZ 3.1	70	38,917	618,790	28.9	241,110	16.6	169,169	71,941	\$312,000
BZ 3.1A	43	4,200	39,927	28.5	17,079	23.0	15,103	1,976	\$9,000
BZ 4.1	33	21,413	206,353	26.0	83,324	12.3	44,457	38,867	\$169,000
BZ 4.1A	5	558	5,258	25.3	2,360	15.4	1,340	1,020	\$4,000
<b>cGMP Total:</b>	<b>172</b>	<b>69,647</b>	<b>930,841</b>	<b>24.9</b>	<b>386,374</b>	<b>17.2</b>	<b>267,377</b>	<b>118,997</b>	<b>\$516,000</b>
Other*	92	213,589	4,294,647	3.2	232,012	<b>w/ 20% Contingency:</b>		<b>95,198</b>	<b>\$413,000</b>
<b>Building Total:</b>	<b>264</b>	<b>283,235</b>			<b>618,386</b>				

\*Primarily unclassified spaces

A consulting company conducted studies that showed potential for reduction of over 297,000 therms of natural gas and over 2,439,000 kWh of electricity, which would result in more than 2,400 metric tons of CO<sub>2</sub> reduction per year. This is over 10% of site energy consumption and GHG emissions, with more than \$400,000 savings per year. The calculation was based on 2018 utilities rates, shown in Table 1, assuming annual cost of energy for each cubic foot per minute (cfm) at \$4.33. This presented a great opportunity to pilot ACR reduction during operation for the entire network.

## Stakeholders and Management

The next step was developing a participation matrix to identify stakeholders and their involvement throughout the project life cycle. Qualification support and internal quality control and validation buy-in were a crucial part for the implementation. The final push was when the site's general manager and head of quality came to the team meeting to endorse the parallel implementation of the change during production.

This show of support from upper site management was both a unifying and liberating factor for several team members who were hesitant to believe we would perform a change and then “run at risk” during a short revalidation period. By removing the age-old constraints for quality, validation, manufacturing, and engineering, the team was able to truly get into the details of the risks and the risk controls we could use.

## Implementation

The overall policy for risk-based activity has been stated in global standards for over 10 years. The questions of risk tolerance are really, “How much risk are we willing to take?” And in scenarios of

higher risk, “Are we to lean toward being risk averse or are we willing to let the data determine true success or failure?” Parallel implementation was chosen due to the following reasons:

- No mechanical modifications were performed on the air handling unit (AHU) to provide reversibility.
- ACRs were not modified in the production areas until the validation of the BZ 4.1 (biozone) nonproduction areas was successfully executed.
- For production areas with open operations, air balancing was not performed during the open operations.
- The successful qualification of the expansion production areas provided additional assurance that operating under reduced ACRs provides a controlled environment that meets Roche/Genentech requirements.

The implementation scope was strictly limited to air balancing. The only way to put the air balance “back the way it was” was to spend the extra time up front, documenting the precise air balance the system had the minute before changes were made. We spent the time to fully survey the airflow at every supply and return grille individually and recorded it by device number. All the air handlers' main ducts for inlet, outlet, makeup, and exhaust were traversed to meet this requirement and to achieve reversibility. This was very useful for pressure balancing because the amount of makeup air remains virtually constant when the recirculation rate decreases. Therefore, the pre-reads with no “physical” modifications provide for complete reversibility.

The second restriction was to perform the changes for the first five of the 15 systems on those where no production activities even occur. These first five systems served a personnel stairwell from

the first floor locker rooms to the second and third floors, first floor corridors, second floor corridors, third floor corridors, and equipment staging and storage areas outside the production rooms. This limits the risk because there is no process or product to be at risk. The other benefit of selecting these first five systems to pre-read, reduce the air balance, and then revalidate first was to build confidence and experience. This was a gate review for showing the project was ready for “prime time” in the production areas.

Each of the 15 cleanroom air systems were a “mini-project” within the overall project. Each required a pre-read air balance, implementation of the new reduced air balance, post-implementation readings for validation of the new configuration, daily sampling for nonviable particulates (NVP), daily sampling for viable air particulates, daily sampling for surface contamination for the revalidation period assessed, and data review by quality control, validation, and quality engineering departments to create final deviation reports for validation and quality engineering approvals, which leads to the next restriction.

Only one of the 15 systems was allowed to be “in process” at any given time. This was beneficial to the overall project in two ways: focus on the team and enabling the team to be smaller. Nothing is more distracting than unfinished or open issues while you are working on something else. Each system got the full attention of the team from start to finish. The team was a consistent set of subject matter experts. Whether for writing the protocols for validation or taking the samples, the same small set of people were involved, which contributed to consistent results. At this point the team has five systems completed, with validation approved, that were returned to service under their belt. They were ready for prime time.

The next restrictions were focused on even more protections for production areas. It started with scheduling of open process activities. For the duration of pre-reads and the implementation of the reduced air balance, that area could not perform any open processing. Once the final validation air balance readings were completed, open operations were allowed “at risk” until the full validation process was completed. Note that sampling is not normally performed during an open process, even for a validated space.

The next change is in added testing because of open operations. For production areas where open activities are performed, a “recovery test” was completed at each location where an open activity occurs during processing. This was done by bringing in specially trained cleanroom certification personnel and allowing them to use a particle generator at each location. The generator was used to spike particles of 0.5 micron just above the ISO 8 limit for the area, then the generator was shut down while an NVP sampling machine recorded the reduction in NVP every 30 seconds until the airborne level reached 10% of the ISO limit, or 1 log reduction. For the test to pass, the area must recover from over 100% to under 10% in a specified time.

In the end, all the restrictions reduced the risk of each and every segment. As we have discussed, some areas are inherently

riskier. Because we needed to formalize this in a GMP change process, we needed a cross-functional team to develop a qualification project plan (QPP) to detail the HVAC equipment (commissioning/operational qualification), environmental monitoring performance qualification strategy, and requirements for existing systems impacted by the HVAC ACR reduction. The team broke the project down into the 15 systems based on areas served by an AHU. The impacted AHUs and areas had individual ACRs as subprojects and thus limited the active scope, and concurrent risk for all aspects, to a single system at any given time.

## RISK ASSESSMENT

A quality risk management report (QRMR) was developed to determine the number of days to perform modified environmental monitoring performance qualification (EMPQ). Under the associated quality risk management plan, the potential risks posed by the ACR on the facility, processing, and/or product were examined and assessed.

The risk assessment process included:

- Data gathering (e.g., room number, HVAC classification diagrams)
- Risk assessment questionnaire to calculate risk score (standard risk matrix)
- Risk matrix for number of days to perform modified EMPQ
- Summarization of risk scoring data



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Figure 4: NVP data for an ISO 7 system (one month average before and after).

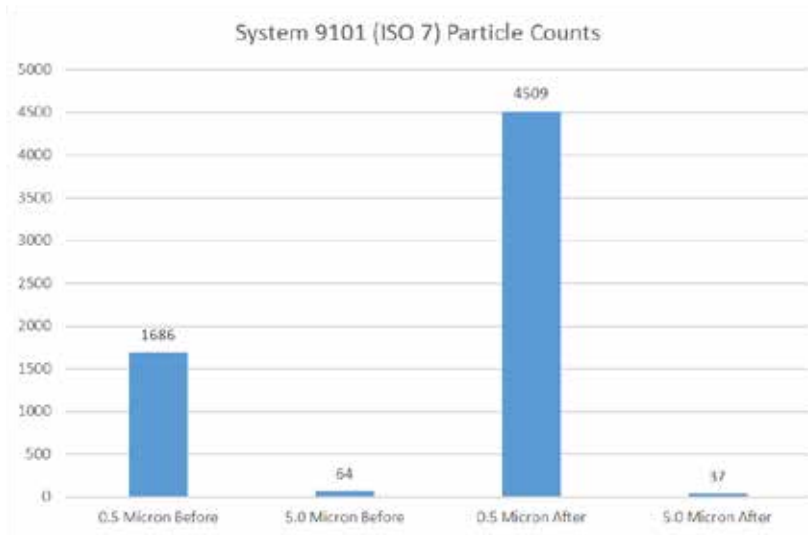
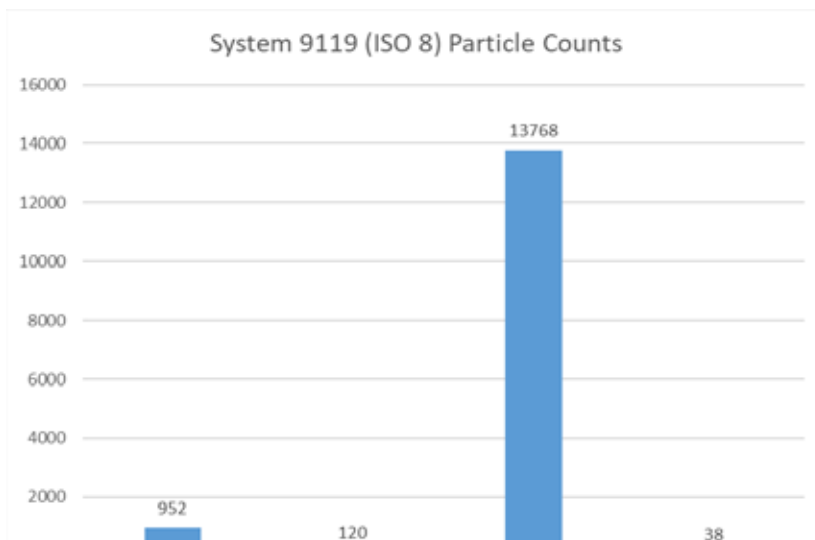


Figure 5: NVP data for an ISO 8 system (one month average before and after).



The team came up with three simple quality categories—low risk, medium risk, and high risk—proving that the distinctions do not have to be fancy or complex.

The quality categories can be broken out as follows:

- Low risk: HVAC systems supplying areas that have no processing. These are primarily corridors and secondarily staging areas for equipment or supplies. Nothing is allowed to be “opened” per standard operating procedure (SOP), as far as product or materials for product.
- Medium risk: HVAC systems supplying processing areas that are closed processes. These are areas where the product or process is fully contained within a tank or piping that is never allowed to be opened per SOP.
- High risk: HVAC systems supplying processing areas that have open processes. Most of these are momentary but still require that the environment be clean enough to meet

the licensed process requirements and not cause contamination that would result in unusable products.

The follow-up for validation was to assign the appropriate number of sampling days for each type of system based on the risk categories:

- Low risk: Requires the least amount of environmental monitoring (EM) sampling and monitoring after the new air balance is completed.
- Medium risk: Requires a moderate amount of EM sampling and monitoring after the new air balance is completed.
- High risk: Requires the largest amount of EM sampling and monitoring after the new air balance is completed and includes special testing of recovery time within three feet of the location where an open process will be performed.

The validation engineer wrote the requalification protocols from these categories. It was agreed that only one system would be qualified at a time. Starting the next system was dependent upon the successful final approval of all validation results.

The new air balance values for all the systems were estimated based on two factors. The first factor is industry research to ensure success is highly likely and starts at more than 10 ACH for ISO 8. The other factor is “turn down” of the existing system and limits to their sizing. Our systems were designed for 25 ACH and so attempting to get down to 6 or 8 ACH was not likely.

We also came across circumstances where rooms could not be optimized down. For example, there was a very long corridor with all south-facing windows. In this case, 10 to 12 ACH would have been optimum, but during the day after the initial balance, both temperature and pressure was unstable in that corridor due to solar gain. We had to increase the ACH to 14 to overcome the solar gain factor. It was combining these factors that allowed engineering and the air balancers to set realistic goals for the area by ISO class:

- Low-risk ISO 8 system: From 25 ACH to 12 ACH +/- 1
- Medium-risk ISO 8 system: From 25 ACH to 14 ACH +/- 1




- High-risk ISO 8 system: From 25 ACH to 16 ACH +/- 1
- High-risk ISO 7 system: 48 ACH to 28 ACH +/- 1

The project was completed in 2020. The implemented changes reduced air flow volume by 165,000 cfm—which was 38% higher than initial estimates presented in Table 1—and resulted in a 14% decrease in energy consumption and GHG emissions and over \$678,000 cost savings per year. With significant energy cost increases in 2021 and 2022, the potential cost savings are much higher than the estimated values.

Figures 4 and 5 show the differences in 0.5- and 5.0-micron particulates found by air sampling before and after the air change reduction for an ISO 7 and ISO 8 (medium risk) system.

## CONCLUSION

This project was a multidisciplinary success, with representatives from manufacturing, scheduling, quality control, quality assurance, validation, facilities, engineering, and project management, as well as HVAC subject matter experts, EM samplers, air balancers, and cleanroom testing certification technicians, all are responsible for the cleanroom environments and yet made a great example of innovative approaches to enable such changes in an environment where continuous production is a key for patients. 

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# INDEX

Adamson Pharma Ltd.	5
COPA-DATA	51
CRB	1
DPS Group	7
El Associates	19
Elettracqua Srl	35
Endress+Hauser Group Services AG	11
Fette Compacting GmbH	Inside Back Cover
Fluor Corporation	Inside Front Cover
GEA Pharma & Healthcare	9
Intelligen, Inc.	47
IPS-Integrated Project Services, LLC	3
Kneat Solutions	Back Cover
STILMAS AMERICAS	23
Sturtevant, Inc.	33
ValGenesis, Inc.	65

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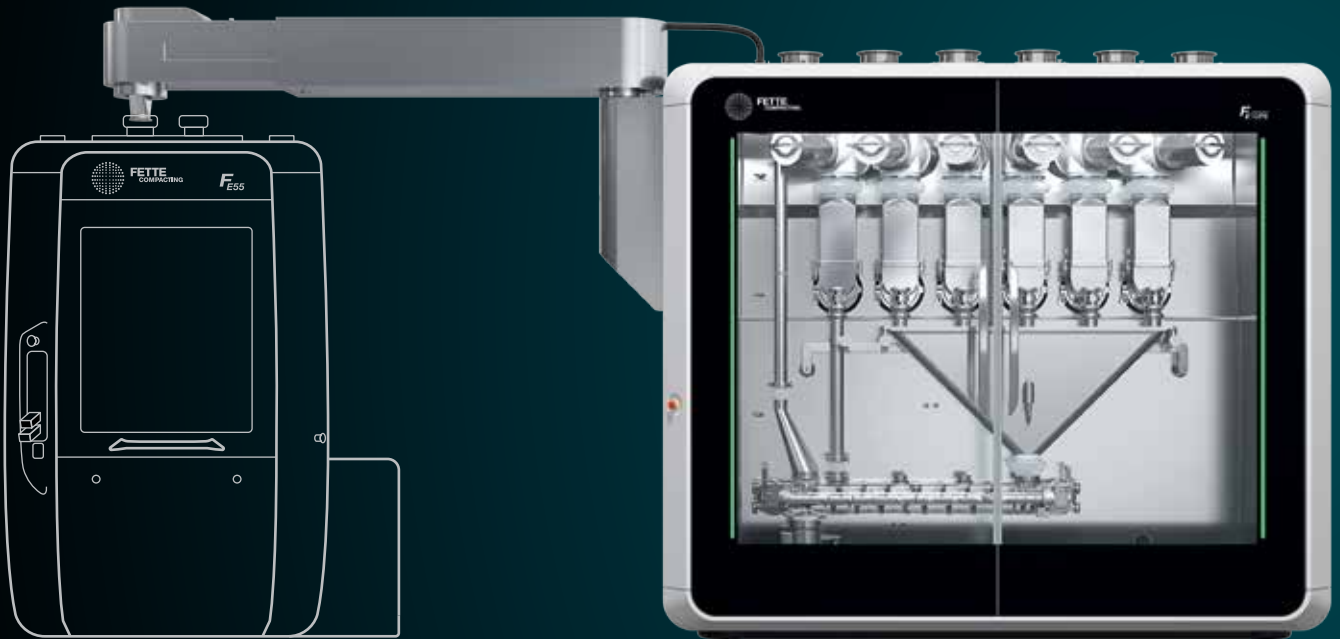
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### Correction to Heeren et al. (2023)

In the article "Methodology to Define a Pharma 4.0™ Roadmap" by Emmie Heeren, Arend Jan Wassink, Venkateshwar Rao Nalluri, and Sebastian Niederhauser (*Pharmaceutical Engineering*, 2023, Vol. 43, No. 3, pp 56-63. <https://ispe.org/pharmaceutical-engineering/May-June-2023>), there was an error in the About the authors section. The biography for Arend Jan Wassink should have read:

Arend Jan Wassink is a Lead Manufacturing & Process Engineer in Digital Manufacturing and Validation at Cpggemi Engineering based in The Netherlands focusing on operational technology, Automation and IoT. He has a bachelor's degree in business informatics and has over 30 years of experience in various IT roles and is 20 years active in the pharmaceutical industry. He is co-chair of the ISPE Pharma 4.0 Process Maps & Critical Thinking Subcommittee. He has been a member of ISPE since 2019.



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