PHARMACEUTICAL ENGINEERING®

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REGULATORY TRENDS & QUALITY INITIATIVES

Mobile Manufacturing in Pharma: Promise, Progress, and Practicalities

Streamlining Post-Approval Changes: Industry Insights on ICH Q14

Readiness for Implementation of ICH Q2(R2) & Q14: Industry Survey Results

CASE STUDIES

Harmonizing Global Innovation: Five Case Studies

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20 MOBILE MANUFACTURING IN PHARMA: PROMISE, PROGRESS, AND PRACTICALITIES

Technological innovations like process intensification, continuous manufacturing, and 3D printing are enabling transportable and point-of-care (PoC) medicines manufacturing—especially for personalized therapies such as cell and gene therapies and ATMPs. These flexible systems offer supply chain advantages but face regulatory and scalability challenges.

28 STREAMLINING POST-APPROVAL CHANGES: INDUSTRY INSIGHTS ON ICH Q14

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40 READINESS FOR IMPLEMENTATION OF ICH Q2(R2) AND Q14: INDUSTRY SURVEY RESULTS

ICH Q2(R2) and Q14 offer modern strategies for analytical procedure development, validation, and lifecycle management. ISPE's 2024 survey highlights industry readiness and areas needing sponsor-regulator alignment. While opportunities abound, challenges persist. Ongoing collaboration is essential to maximize regulatory efficiency and improve analytical procedure implementation and maintenance.

IN THIS ISSUE: As regulatory trends and quality initiatives continue to evolve in the pharmaceutical industry, this issue examines industry rules that support continuous improvement across the product lifecycle.

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ISPE successfully assisted Health Canada with International Council for Harmonisation (ICH) Q13 implementation training in virtual sessions with 170 participants in attendance.

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Jeffrey A. Biskup, PE

Exploring Regulatory Trends and Quality Initiatives with ISPE

ISPE is proud to celebrate its 45th anniversary of working with regulators and professionals from across the industry and around the world to shape the future of pharma. This year also marks the 20th anniversary of the ISPE Facility of the Year Awards (FOYA), which celebrates extraordinary achievements in pharmaceutical manufacturing.

Our September/October issue focuses on regulatory trends and quality initiatives. ISPE is continually striving to enhance our regulatory engagement efforts. We recognize the importance of regulatory affairs and continue to build and strengthen our relationships with health authorities on behalf of our members.

ISPE REGULATORY AFFAIRS OVERVIEW

With more than 2,200 ISPE members from regulatory authorities representing 76 countries, ISPE has a strong regulatory presence. In 2024, ISPE secured 96 regulatory speakers across 23 events, more than 350 regulatory attendees from 44 countries, and regulatory reviews of seven ISPE Guidance Documents.

Our 17 Regulatory Volunteer Groups work to strengthen relationships and collaborative efforts with global regulatory authorities. In 2024, 290 members contributed to more than 50 conference sessions, articles, blog posts, and more. They also

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provided expert input on 12 documents released for consultation.

Members of ISPE's committees, working groups, and initiatives are involved in training activities with health authorities to support the implemention of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. For example, in April, ISPE provided training to Health Canada on implementing ICH Q11.

KEY ISPE REGULATORY AND QUALITY INITIATIVES

ISPE's Enabling Pharmaceutical Innovation Program

This program promotes global harmonization of regulatory guidelines to improve patient access to innovative medicines and technologies. In response to regulatory interest, ISPE has shared case studies highlighting industry challenges and continues to engage with health authorities to support alignment. Over the past decade, inconsistent interpretation of ICH guidelines across regions has hindered innovation in manufacturing and continuous improvement. Learn more in the article "Delivering for Patients Through Harmonization: Insights from Five Global Innovation Case Studies," on page 48.

ISPE's Advancing Pharmaceutical Quality (APQ) Program

This program helps organizations assess and improve their quality management maturity (QMM) using practical tools aligned with global standards and priorities of the US Food and Drug Administration (FDA). The program supports global quality excellence and aligns with the US FDA's focus on QMM to assess and rate the maturity of manufacturing facilities. The ISPE APQ Guide Series covers key areas like change management, Corrective Action and Preventive Action (CAPA) systems, management responsibilities and review, performance and product quality monitoring systems, and cultural excellence. ISPE also offers a training course based on the guide series. Looking ahead, ISPE is developing a Quality Risk Management (QRM) maturity assessment tool in collaboration with APQ, drug shortages, and QRM teams, expected in 2026.

ISPE's PQLI® Initiative

This initiative started as a way to help bring the ICH quality guidelines to life—making them practical and actionable for the industry. It focuses on key concepts from ICH Q8 through Q12 to support product quality throughout its lifecycle, with the goal of driving continuous improvement.

ISPE's PQLI® technical teams are developing solutions to help the pharmaceutical industry keep up with changing regulations and scientific advancements. Specifically, they're focused on areas like Chemistry, Manufacturing, and Controls (CMC) and Good Manufacturing Practices (GMP). By developing new approaches in these areas, the teams aim to help companies maintain high product quality and stay compliant with evolving global standards. Learn more at ISPE.org/initiatives/PQLI.

ISPE provides on-demand, self-paced training covering ICH Guidelines 6–10, supporting education in pharmaceutical development and manufacturing. For details, visit ISPE.org/training. To learn more about ISPE's regulatory and quality initiatives, visit ISPE.org/regulatory.

Jeffrey A. Biskup, PE, is the Executive Chairman of the Board at Clark, Richardson and Biskup, Consulting Engineers Inc. (CRB) and the 2024–2025 ISPE International Board Chair. He joined ISPE in 1998.

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By Edyna Miguez


Edyna Miguez

GET INVOLVED WITH WOMEN IN PHARMA® THIS FALL

As fall approaches, it brings with it one of the most anticipated events in our industry: the 2025 ISPE Annual Meeting & Expo. More than just a conference, it's a dynamic gathering where pharmaceutical professionals from around the world come together to exchange ideas, explore innovations, and strengthen our global community.

This year's meeting takes place 26–29 October 2025 in Charlotte, NC, US, and online. Whether you'll be joining in person or virtually, ISPE's Annual Meeting & Expo is your chance to engage with thought leaders, grow your network, and be part of shaping what's next in pharmaceutical science.

As always, Women in Pharma is excited to take on the week with a full slate of programming designed to inspire, connect, and empower. From a transformational workshop and our signature Monday night event to mentoring opportunities and committee planning sessions, Women in Pharma invites you to be part of an impactful experience that continues to expand what leadership and community look like in our industry. Our presence at ISPE's Annual Meeting & Expo represents the culmination of a year of collective momentum—and an invitation to everyone committed to building a more supportive industry. We hope you'll join us in Charlotte to reflect, connect, and help shape the next chapter. Here's everything you have to look forward to.

WOMEN IN PHARMA SUNDAY WORKSHOP

In an industry driven by innovation and precision, many people struggle with self-doubt, career transitions, and the quiet assumption that great work should speak for itself. This transformational Women in Pharma Workshop will help participants challenge imposter syndrome, reflect on personal and professional identity, and gain tools to confidently navigate career evolution.

Led by Charlotte-based executive coach and leadership expert Jessica Bronzert of The Sparks Group, the session will draw on insights from the acclaimed books *Working Identity* by Herminia Ibarra and *Finding Your Own North Star* by Martha Beck. Through a dynamic blend of keynote insights, interactive discussion, and a powerful panel of leaders, attendees will be inspired to own their voice, reimagine success, and take strategic action in their careers.

Whether you're facing a crossroads or simply seeking greater alignment between your passion and your profession, this workshop is your starting point for purposeful progress.

What You'll Gain:

- A deeper understanding of imposter syndrome—what it is, how it manifests, and strategies to overcome it
- A framework for making confident, value-based career shifts
- Insights into self-promotion and visibility from a gender-lens perspective
- Stories of real women navigating career pivots successfully
- Community connection and inspiration to take your next bold step

Workshop Panelists:

- Thomas Carganico: VP Strategic Development, Marketing & Communication, Partner, PQE Group
- Lineke Pelleboer: Director of Business Development, Batavia Biomanufacturing
- Tanya Sharma: Co-Founder, Assurea LLC

WOMEN IN PHARMA MONDAY NIGHT EVENT

The Women in Pharma event "A Walk in Their Shoes: Legends, Leadership and the Ones Who Paved the Way" will take place Monday 27 October, 7:30–10:00 pm ET. This year's signature event promises an evening of reflection and celebration at an off-site jazz club, where timeless elegance meets bold inspiration. Attendees will step into the stories of trailblazing women and industry allies whose courage and leadership helped shape the pharmaceutical landscape. Through curated storytelling, interactive group conversations, and collaborative table activities, participants will honor the legacies of those who came before while building meaningful new connections.

Registration fees:

- $75 for industry members
- $50 for emerging economies, students, and recent graduates

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By Rebecca Roscher


Rebecca Roscher

MAINTAINING QUALITY REQUIRES "QUALITY THINKING"

"Excellence, then, is not an act, but a habit," wrote the historian and philosopher Will Durant. However, when considering habits of excellence, or quality, we ought to first consider the origin of these habits. These habits originate from our thought patterns and are the architects of our actions. This means that quality actions begin with quality thoughts.

Quality of thought is more than a philosophical ideal; it represents the caliber and precision of an individual's thinking processes. It gauges how clearly, logically, and creatively we reason when faced with complex problems or when generating new ideas. This concept has ancient roots and has evolved throughout time by incorporating aspects of psychology (highlighting cognitive clarity and bias reduction), philosophy (emphasizing sound reasoning and critical analysis), and engineering (focused on systematic problem-solving).

It is closely related to both critical thinking (evaluating information and arguments methodically) and creative thinking (innovating and finding novel solutions). A high quality of thought means one's cognitive approach is thorough, well-structured, and imaginative, laying a foundation for effective problem-solving and sound decision-making.

Some forms of thinking might be better suited for certain tasks. Kahneman's cognitive model, for instance, differentiates intuitive (System 1) from reflective and analytical thinking (System 2), emphasizing the latter's advantage for thoroughly addressing complex quality and regulatory scenarios.

However, the following general definition of quality thought applies to all scenarios: Focusing on high-quality thinking enables a culture of intellectual rigor, facilitating risk assessments, root cause analyses, and deviation handling as well as overall problem-solving. That rigor allows for successful actions like establishing preventive measures, continuously optimizing operations, and making on-point strategic decisions regarding project pipelines and investments.

Ronald Howard, the late Stanford University professor and pioneer in decision analysis said, "Clarity of action depends on quality of thought. You have to get your thinking straight before you can talk about making choices." Pharmaceutical professionals must frequently deal with substantial regulatory documentation, data-rich clinical studies, and sometimes even mysterious quality issues. For companies in the pharmaceutical, biotechnology, and life sciences fields, it is worthwhile to invest in cognitive trainings because they equip employees and team members with superior analytical skills, significantly reducing cognitive biases that could lead to regulatory oversights or quality deficiencies. To outline this, I would like to share a few examples of what is already being undertaken by today's industry.

Mandatory AI Training

This year Johnson & Johnson implemented mandatory training for AI usage, ensuring widespread AI literacy within the organization. We could think about implementing structured critical thinking methodologies like the Paul-Elder framework as well, guiding professionals to assess their cognitive processes rigorously against intellectual standards such as clarity, precision, depth, logic, and fairness.

Creative Problem-Solving

Companies like Pfizer help foster creative problem-solving using methods like design thinking to encourage patient-centered innovation and compliance solutions. Another robust alternative is the theory of inventive problem solving (TRIZ), which has demonstrated effectiveness in improving adverse event reporting, deviation management, and precision medicine innovation.

Games and Challenges

Eli Lilly's AI Games and ISPE's Hackathons are examples of organizations offering games and challenges that inspire innovation and critical thinking. Leveraging humans' competitive nature is a playful way to get people passionate about current issues and familiarized with existing tools.

Focus Time

Another option is enforcing focus times, like Takeda's meeting-free Fridays. Institute structured "deep-thinking sessions," free from interruptions, to enable focused evaluation of complex

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Lou Schmukler

LEADER AS ROLE MODEL: An Example from History

There is a dated leadership model known as the "Great Man" theory. It posits that history has been largely shaped by highly influential and exceptional individuals who, through natural attributes such as superior intellect, heroic courage, and outstanding leadership skills, have had a decisive impact on historical events.

In my opinion, a figure who best represents this theory is Alexander the Great, one of history's most legendary conquerors. He lived during the mid 4th century BC and, in just 32 years, created one of the world's largest empires—stretching from Greece and Egypt to northwest India. He was schooled by Aristotle, the renowned ancient Greek philosopher and polymath. Crowned king at the age of 20, Alexander was undefeated in battle and is widely considered one of the greatest and most successful military commanders to ever live. His military prowess and strategic genius remain subjects of study in military academies around the world.

THE LEADERSHIP OF ALEXANDER THE GREAT

From a leadership perspective, few compare to Alexander. Although not without his faults, he demonstrated essential leadership lessons that remain relevant today. Alexander was a visionary. He executed strategy flawlessly, surrounded himself with a talented and well-rounded team, encouraged innovation, prioritized organizational governance, and focused on development and succession. Time and again, he inspired and motivated his army to achieve the impossible. Remarkably, given the era, he emphasized diversity and inclusion as his empire expanded—qualities we continue to instill in leaders today.

One of Alexander's leadership traits worth further examination is what best-selling business authors James M. Kouzes and Barry Z. Posner call "Modeling the Way."

MODELING THE WAY

What does it mean to Model the Way? It refers to the example a leader sets for others—embodying the leadership qualities most admired. It involves building team consensus, enforcing agreed-upon standards and principles, requesting feedback, and following through on commitments. Some might call this "walking the talk."

A key requirement for being a great role model is having a clear leadership philosophy and a strong set of values to guide actions and decisions. Every leadership journey begins with self-awareness—knowing what you believe in, what you stand for, and what matters most. Leadership is easiest when things are going well. It's during adversity that being a role model matters most. Remaining honest, competent, inspiring, and forward-looking when facing tough times is when it's of the utmost importance. It means keeping your head while those around you are losing theirs.

ALEXANDER AS ROLE MODEL

Alexander exemplified "Modeling the Way" in many ways. He was a leader who literally led from the front, often at great personal risk. He never asked his men to do anything he wouldn't do himself. His army trusted him implicitly and literally followed him to the ends of the earth.

Alexander fostered organizational cohesion and communicated in the simple language of his soldiers, which had a captivating influence on all who heard him. He made extensive use of powerful cultural symbols that evoked strong emotions. These meaningful actions, combined with his talent for leading by example, fostered strong group identity and motivated his troops to go above and beyond.

Alexander shared in the hardships of his army. One well-documented example occurred during a forced march through the desert, when the army faced a severe water shortage and many died of thirst. His men reserved a portion of the remaining water for him, but Alexander refused it, choosing to share in their burden. On another occasion, during an assault on an enemy fortification, his army was stalled and believed they were at a stalemate. To inspire them, Alexander scaled the wall himself and leapt to the ground.

Surrounded by the enemy and seriously wounded, Alexander's actions inspired his army to follow him, ultimately leading them to victory. He was deeply loved by troops, a sentiment born out of their respect for him and the example he set.

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CONTINUED FROM PAGE 8, WOMEN IN PHARMA

Space is limited, and separate registration is required. Register for the 2025 ISPE Annual Meeting & Expo at ISPE.org/Conferences/2025-Annual-Meeting-Expo

WOMEN IN PHARMA GLOBAL COMMITTEE MEETING

The Women in Pharma Global Committee Meeting will be held at 12 PM (EST) on 29 October at the close of the ISPE Annual Meeting & Expo. To register, email emiguez@ispe.org

MENTOR ISPE: APPLICATIONS NOW OPEN

Whether you are just starting out or looking to pay it forward, Mentor ISPE is your opportunity to grow through intentional mentoring and global community support. This structured program connects mentors and mentees for a shared journey rooted in collaboration, trust, and professional development. Applications close 1 November 2025. Learn more at ISPE.org/Women-Pharma

JOIN THE INTERNATIONAL STEERING COMMITTEE

Ready to lead? Apply to join the Women in Pharma International Steering Committee and help guide global strategy, shape future programming, and expand our impact across the industry. Applications close 30 September 2025. Email WIP@ISPE.org for details. Let's make this a season of connection, collaboration, and lasting impact. To learn more about ISPE's Women in Pharma, visit ispe.org/women-pharma

Edyna Miguez is the Membership Growth Manager for ISPE.

CONTINUED FROM PAGE 9, EMERGING LEADERS

regulatory documents, risk assessments, and quality strategies. Case studies in the pharmaceutical industry have validated this approach, linking enhanced cognitive quality with improved regulatory outcomes and quality assurance.

Agile Organizational Structures

Creating agile organizational structures like Bayer's Dynamic Shared Ownership model is another successful example. Flat hierarchies and dynamic team configurations promote individual accountability and decision-making, enhancing the collective quality of thought.

A COMPETITIVE FACTOR

What initiatives is your organization or ISPE Chapter implementing to nurture the quality of thought? How can each professional contribute to fostering a cognitively rigorous environment? In the pharmaceutical context, quality of thought is far more than a buzzword—it is a decisive competitive factor. Scientific definitions from psychology and cognitive research make "good thinking" tangible. Its importance is evident every day in pharmaceutical practice, where the power to innovate and solve problems determines success.

Proven methods allow companies to nurture high-quality thinking deliberately, and best-practice examples show how such a mindset can be embedded in corporate culture. Multiple studies confirm the effectiveness of these approaches. Investing in superior thinking—through training, culture, and organizational structures—pays off in better ideas, more efficient processes, and, ultimately, more successful therapies for patients.

"Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution. It represents the wise choice of many alternatives," author unknown (this quote is commonly attributed to the World War II veteran and Medal of Honor recipient William A. Foster or early 20th century economist William Trufant Foster).

About the author

Rebecca Roscher, MSc, is a Project Manager at GP Grenzach Production GmbH, a Bayer-owned production facility in Grenzach-Wyhlen, Germany. As the ex officio member of the ISPE International Board of Directors for 2024–2025, Rebecca represents and advocates for the interests of young professionals as part of the ISPE Emerging Leaders Community of Practice. She joined ISPE in 2020.

CONTINUED FROM PAGE 10: GUEST COLUMN

AN UNFORTUNATE ENDING

The story of Alexander the Great is an incredible one. He began his reign as an enlightened leader and an remarkable role model. However, as time went on, he became addicted to power, increasingly domineering and unforgiving. As he grew less tolerant and unaccepting of any criticism, his leaders kept their reservations to themselves. His leadership progressively degenerated in the eyes of his men.

He died in Babylon (modern-day Iraq) at the end of a 12-year campaign, never again to return to his homeland. This unfortunate ending does not take away from his extraordinary achievements. Alexander left a permanent mark on the world. He will remain a figure of fascination and study for thousands of years after his death, and even today, we can still learn valuable lessons from his leadership style.

Lou Schmukler served as Executive Vice President and President of Global Product Development and Supply at Bristol Myers Squibb until his retirement. His pharmaceutical industry career spanned over 40 years. He holds a BS from Temple School of Pharmacy and an MA from Webster University. He joined ISPE in 1993.

By Brandon Pastore

ISPE LAUNCHES THE ISPE ACADEMY


Brandon Pastore

NAVIGATING A CAREER IN PHARMACEUTICAL ENGINEERING: A 30-Year Journey into the Future

When I began my journey in the pharmaceutical industry over 25 years ago, the environment was markedly different from what we see today. We operated in a world dominated by paper-based systems, outdated training videos from the 1980s, and a heavy reliance on self-directed reading. Career progression was more about navigating an informal ladder—gaining experience, demonstrating capability, and acquiring knowledge through hands-on exposure—rather than following a structured curriculum.

There were general expectations and milestones that guided advancement, but no clearly defined learning paths or standardized courses to prepare you for the next opportunity. Today, the industry has evolved into a highly regulated, data-driven, and technologically sophisticated space. Success now requires not only deep domain expertise but also a proactive commitment to continuous learning and adaptability.

The pharmaceutical industry has undergone a seismic shift. The integration of automation, digital twins, AI-driven analytics, and continuous manufacturing has redefined how we design, operate, and optimize facilities. Regulatory expectations have evolved in parallel, with agencies now encouraging innovation while maintaining a laser focus on patient safety and product quality. As a result, the role of engineers and manufacturing professionals has expanded. We are no longer just problem-solvers—we are innovators, data scientists, and strategic thinkers.

This transformation has brought with it a new challenge: staying current. The pace of technological advancement is relentless. What was cutting-edge five years ago is now standard practice, and what's standard today may be obsolete tomorrow. For professionals like me, who have spent decades in the industry, this means embracing a mindset of lifelong learning. It's not enough to rely on experience alone; we must continuously update our knowledge and skills to remain effective and relevant.

> "Whether you're aiming to advance your career, adapt to emerging technologies, or simply keep pace with the rapid changes shaping our work, the ISPE Academy is a powerful resource."

That's why I'm excited about the ISPE Academy. As someone who has dedicated a career to this ever-evolving field, I see the ISPE Academy as a transformative step forward. It recognizes that learning doesn't end with a degree—it's a lifelong pursuit. In an industry as dynamic and consequential as pharmaceutical engineering and manufacturing, staying current isn't optional; it's essential.

Whether you're aiming to advance your career, adapt to emerging technologies, or simply keep pace with the rapid changes shaping our work, the ISPE Academy is a powerful resource. It's more than professional development—it's a strategic investment in your future and in the continued progress of our industry.

INTRODUCING THE ISPE ACADEMY: A NEW ERA OF LEARNING

The ISPE Academy is a timely and much-needed initiative designed to support professionals in the pharmaceutical industry through high-quality, accessible, and industry-relevant education. Developed by ISPE, the Academy offers a structured platform for continuing education that aligns with the needs of our field.

How does it work?

The ISPE Academy provides a curated catalog of online courses, certificates, and learning paths that cover a wide range of topics—from foundational GMP principles to advanced subjects like GAMP®, data integrity, and biopharmaceutical manufacturing. Courses are developed and taught by industry experts, ensuring that the content is both practical and current.

Why now?

The timing couldn't be better. As the industry grapples with workforce shortages, rapid innovation, and increasing regulatory complexity, there is a growing need for scalable, high-impact training solutions. The ISPE Academy addresses this gap by offering a centralized resource for upskilling and reskilling. It's not just about compliance anymore—it's about building a workforce that can lead the next wave of pharmaceutical innovation.

What's the benefit?

The ISPE Academy offers a clear path to career advancement. Whether you're early in your career or a seasoned professional, the ability to demonstrate up-to-date knowledge and competencies is invaluable. For companies, it provides a consistent and cost-effective way to train teams, reduce knowledge gaps, and ensure alignment with industry best practices. Several companies have already integrated ISPE's courses into their internal training programs, recognizing the value of standardized, high-quality content.

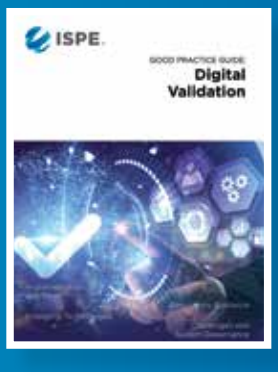
For more information, email ask@ispe.org or call +1-813-960-2105.

Brandon Pastore is Senior Director of Professional Development at ISPE. He brings extensive experience from roles at Catalent Pharma Solutions, Bausch + Lomb, and Pfizer, including leadership in global R&D and technical services. A skilled continuous improvement leader, Brandon has expertise in FDA compliance, GMP, validation, analytical chemistry, and HPLC. He holds a BS in Chemistry from La Roche College and has a strong track record in pharmaceutical manufacturing and operational excellence.



VALIDATION 4.0 FOR THE PHARMACEUTICAL INDUSTRY

By Marcy Sanford



The pharmaceutical industry is under increasing pressure to develop new therapies at a faster pace, while lowering drug costs, enhancing quality, and maintaining safety and a robust supply chain.

Validation 4.0 ensures that validation processes are not a bottleneck but a strategic enabler of innovation, quality, and compliance by embracing artificial intelligence (AI), Internet of Things (IoT), cloud computing, and digital twins utilizing the foundational aspects of quality by design (QbD), quality risk management (QRM), and knowledge management. However, many companies have not adopted flexible approaches and embraced the possibility of Validation 4.0, despite two decades of recommendations from regulators in both the US and Europe. The recently published *ISPE Good Practice Guide: Validation 4.0* is intended to be an introduction into modern validation thinking in an increasingly digital world that offers new capabilities for managing and controlling manufacturing processes.

"We are at a critical inflection point," said Guide Co-Lead, Michelle Vuolo, Head of Quality, Tulip Interfaces. "Both the processes and the possibilities are evolving, and faster than ever before. Oftentimes industry remains entrenched in conventional methodologies for achieving and sustaining compliance, particularly concerning our validation practices. Validation 4.0 aims to comprehensively examine the quality infrastructure including existing guidances and regulations and demonstrate their implementation in a digital environment. The underlying objective is to facilitate rapid evolution while maintaining verifiable control over products and processes. This approach represents a paradigm shift in validation, moving from a project-based methodology or a fixed number of validation runs toward a more efficient generation of evidence to demonstrate control within the digital realm."

Based on existing QbD, QRM, and holistic control strategy (HCS) principles as described in the *ISPE Baseline® Guide: Pharma 4.0™*, and the intention of the draft US Food and Drug Administration (FDA) guidance on 211.110 to enable flexibility in adapting processes to ensure product quality throughout the product's lifecycle, the Guide was developed by a global team of experts. The *ISPE Good Practice Guide: Validation 4.0* provides an overview of methodology considerations, covers foundational enablers and required capabilities, and presents case studies to facilitate successful integration when adopting Validation 4.0 in manufacturing operations.

> "We are at a critical inflection point—both the processes and the possibilities are evolving, and faster than ever before."

As validation practices and paradigms shifted throughout the industry's prior evolutions, they must now adapt once again to meet the demands of shifting industry expectations. Despite the introduction of QRM and QbD principles, their adoption has often been limited in scope and depth. Without meaningful progress, organizations risk facing significant challenges in implementing legacy validation approaches for innovative therapies such as personalized medicine, biopharmaceuticals, and continuous manufacturing that require more adaptive processes.

"Digital essentially enables the capability to identify, monitor, and react to risks and associated control strategies at the data level on a real time basis, and to help us move away from point in time validation, ultimately enabling faster time to market and a continual improvement culture," said Vuolo.

Achieving this with balance, demands scalable productivity solutions, particularly through automation and integrated systems. As organizations deal with increasing data volumes, so does the need for robust data quality and integrity not only for GxP purposes. This requirement extends into applications of emerging technologies, such as artificial intelligence and machine learning. If legacy validation practices persist, a hindrance will be seen in the pharmaceutical sector's ability to keep pace with modern data analytics to accelerate innovation and improve outcomes.

For more information, visit ISPE.org/publications/guidance-documents

NEW GAMP® GUIDE ADDRESSES CHALLENGES POSED BY AI-ENABLED COMPUTERIZED SYSTEMS

By Brandi Stockton, Eric Staib, and Martin Heitmann



The new *ISPE GAMP® Guide: Artificial Intelligence* provides a comprehensive, state-of-the-art best practice framework to efficiently and effectively achieve high-quality AI-enabled computerized systems in regulated life science areas. It bridges established GAMP® concepts with characteristics of AI and complements other GAMP Guidance Documents.

Since 2019, members of the GAMP® Community of Practice (CoP) Software Automation (SA) and Artificial Intelligence (AI) Special Interest Group (SIG) have collaborated and consistently produced guidance to support practical implementation of AI-enabled computerized systems. By the summer of 2023, only a few months after the release of GPT-3 (the third-generation Generative Pre-trained Transformer), GAMP SA and AI SIG Leaders were inundated with questions, indicating a rise in concern, and the growing set of challenges our industry colleagues were facing. We agreed that it was time to create a GAMP® AI Guide to enable companies to efficiently and effectively implement AI-enabled computerized systems.

Life science professionals around the world shared their concerns and expressed their fears as they struggled to understand technology and sought guidance. Only a limited number of pioneers within industry and ISPE were collaborating on AI topics, many from the GAMP CoP. The members of the GAMP SA and AI SIG representing this group of pioneers were flooded with questions asking how, if at all, AI could be validated. From these discussions, several recurring themes and key challenges emerged:

- **Knowledge management**: the need to build AI literacy skills
- **Evolving regulatory expectations**: regulatory uncertainty from a lack of clear guidance
- **Suppler relationships**: lack of common language and clarity on responsibilities
- **Pace of innovation**: rapid technological advances outpacing organizational readiness
- **Risk management**: uncertainty in determining an appropriate control strategy by lack of technology understanding
- **Data**: often fragmented, collected, and structured for its intended purpose that may not be fit for the purpose of AI development
- **Cybersecurity**: new cybersecurity threats aiming to exploit the dependency on data and complexity of models
- **Legal considerations**: connecting the wider legislative landscape, including cross-sector AI regulation and established statues, e.g. concerned with data privacy

The result of these challenges: Too many AI initiatives failed or stopped at pilot stages. The failure rate of AI projects is estimated at 80%, which is considerably higher than general IT projects 10 years ago [1]. These projects originating from a need or an opportunity aiming for tangible benefits, such as: Higher efficiency in helping to manage increasing workloads, improved support for patients through AI-enabled devices, better process control, and yield increase in pharmaceutical manufacturing, among others. Each project failure in these areas is not only a loss of investment resources but in many cases also has consequences for patients. The same being true for AI-enabled systems in operation that lack robustness, reliability, and control. It was time for a change.

The recently published *ISPE GAMP® Guide: Artificial Intelligence*, addresses challenges posed by AI-enabled computerized systems in the pharmaceutical and medical device industries. It offers a cost-effective, best-practice framework to help ensure these systems are high-quality, effective, fit for intended use, and comply with relevant regulations. It is meant to facilitate a common understanding of AI's possibilities and limitations within GxP-regulated environments. It serves as a reference point for stakeholders— including regulated companies, suppliers, service providers, and regulators—on best practices in developing, implementing, and using AI-enabled systems. With a primary focus on quality and compliance, the Guide supports innovation in settings where patient safety, product quality, and data integrity are paramount. It covers both managerial and organizational topics, as well as technical aspects.

Users of the Guide can harness various business benefits:

- Facilitating risk-based approaches in conjunction with enabling innovation to allow for focusing efforts and allowing for efficiency while achieving compliance
- Supporting organizations in choosing system designs that fit the organization's overall maturity and level of experience
- Having a common language to support collaboration across diverse stakeholders as a key factor in improving successful

implementation of AI-enabled computerized systems
- Establishing an effective monitoring and maintenance strategy, while demonstrating ongoing control
- Facilitating continual improvement during operation, particularly by using newly generated data

With a shared framework provided by the *ISPE GAMP® Guide: Artificial Intelligence*, industry can streamline processes in the design, implementation, and use of AI-enabled computerized systems. This enables the maintenance of patient safety, improved efficiency through risk-based approaches, application of critical thinking, and opportunities for continuous improvement.

This Guide is useful to a broad set of stakeholders:
- GxP regulated companies (e.g., in the areas of pharmaceuticals, biologics, advanced therapy medicinal products, or medical devices)
- Suppliers (e.g., equipment, hardware and software)
- Service providers (e.g., contract research organizations, contract development and manufacturing organizations, contract testing laboratories or specialty labs)
- Consultancies supporting other organizations in the design, implementation, and use of AI-enabled computerized systems

Additional stakeholders may include academia and healthcare providers involved in regulated activities or committed to safeguarding patient safety, product quality, and data integrity. The Guide is also relevant to those engaged in early research outside traditional GxP-regulated areas.

Regulators and healthcare authorities may find the Guide a valuable reference for understanding industry perspectives on best practices for AI. By offering a holistic view of achieving high-quality AI-enabled computerized systems in GxP regulated environments, the Guide serves as an industry response to recent discussion and reflection papers published by regulatory and health authorities. Selected regulatory initiatives include:
- US Food and Drug Administration (FDA) Center for Evaluation and Research *Artificial Intelligence in Drug Manufacturing* [2]
- US FDA *Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products – Discussion Paper and Request for Feedback* [3]
- European Medicines Agency (EMA) *Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle* [4, 5]
- US FDA *Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products* (Draft Guidance) [6]
- US FDA *Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations* (Draft Guidance) [7]

ALIGNMENT WITH ESTABLISHED GUIDANCE AND STANDARDS

The new Guide bridges general concepts of *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* [8] with the characteristics of AI, expanding on considerations provided in Appendix D11 to achieve a holistic framework. Guidance such as *ISPE GAMP® Guide: Records and Data Integrity* [9], and the *ISPE GAMP® Records and Data Integrity Good Practice Guide: Data Integrity by Design* [10] have been incorporated in the new *ISPE GAMP® Guide: Artificial Intelligence*. The Guide considers current industry regulation and guidance as well as available standards and frameworks, such as ISO/IEC 42001:2023 [11].

CONCEPTS DEVELOPED IN THIS GUIDE

The Guide aims to define the overarching framework for developing and using AI-enabled computerized systems, introducing extensions to existing guidance, new concepts, and practical details:
- **Risk management:** Quality Risk Management (QRM) is central to ensuring patient safety, product quality, and data integrity. The Guide outlines AI-specific risk considerations and a framework for identifying and controlling risks.
- **Scalable life cycle activities**: Promoting a risk-based approach and use of critical thinking, the Guide encourages scalable life cycle activities.
- **Regulated company and supplier collaboration**: Guidance is provided to enhance supplier assessment and monitoring in the context of AI-enabled systems.
- **Roles and responsibilities**: The Guide addresses evolving roles and responsibilities, augmenting existing ones and introducing new roles. It highlights quality assurance unit (QAU) activities that support decision-making and ensure compliance of AI-enabled computerized systems.
- **Data and model governance and management**: The Guide introduces concepts like fit-for-purpose data, considerations on data quality, and an extended view on data governance to build robust data foundations. Model governance strategies further ensure decision traceability throughout development and use.
- **Ideation, design, and proof-of-concept:** To support AI project setup, the Guide outlines key concept-phase elements, including proof-of-concept components that form the foundation for transitioning to the project phase.
- **Model development:** The Guide provides model development guidance, covering key steps, risks, decision-making, and documentation throughout the life cycle.
- **Testing of models and AI-enabled computerized systems:** The Guide includes testing approaches for models and AI-enabled systems, using fit-for-purpose data, performance indicators, human assessments of usability and suitability, and considerations for robustness and fairness.
- **Ongoing monitoring:** The Guide considers the use of live data for ongoing monitoring to ensure control and support continual improvement.
- **Change management**: The Guide supports comprehensive decision-making in change management, addressing both business and quality drivers.
- **CAPA management:** The Guide outlines typical incident scenarios, remediation approaches, and incident and Corrective and Preventive Action (CAPA) considerations specific to AI-enabled systems.
- **Knowledge management**: Guidance is provided on integrating

specialized expertise—such as data scientists and ML engineers—into established roles like data and system owners. The Guide also emphasizes AI literacy and strategies for building organizational competencies.

- **Trustworthy AI**: The Guide promotes responsible AI use through transparency, human oversight, and bias mitigation, facilitating responsible and ethical use of AI.
- **Explainable AI**: Guidance is provided to support human-AI-team collaboration in GxP regulated processes.
- **Dynamic systems**: Expanding on *GAMP® 5 (Second Edition)* Appendix D11, the Guide addresses dynamic systems across concept, project, and operational phases.
- **Cybersecurity**: Cybersecurity guidance includes considerations for adversarial attacks on data and models.
- **AI as and in medical device**: The Guide integrates medical device practices—such as design reviews and device-specific risk management—into broader strategies for safe and effective AI-enabled systems.

CONCLUSION AND SUMMARY

Producing the *ISPE GAMP® Guide: Artificial Intelligence* has been an enlightening journey, integrating existing concepts and building a comprehensive understanding of subject matter by close interdisciplinary collaboration. The Guide highlights both the complexity of AI-enabled computerized systems and the value of teamwork across disciplines.

The AI Guide team looks forward to the impact this resource will have in supporting industry implementation of AI-enabled systems. We see the Guide as the beginning of a longer journey. As technology advances, challenges across GxP areas will grow—data volumes will grow, processes will become more complex, and personalized medicine will move closer to reality. We believe that AI can offer means to address these challenges and unlock new horizons in life sciences, if we understand AI as an integral part of a broader digital strategy—not as a one-size-fits-all solution.

We invite all stakeholders to join us in this journey, collaborating, co-creating, and co-inventing the future of life sciences. The ISPE AI CoP and GAMP SA and AI SIG welcome new members.

Figure 1: Overview of new and extended concepts developed in the Guide



References

1. Hanhan, Musa. "Why your predictive analytics and AI projects are failing – and how to transform your success." CX Network. 25 March 2024. https://www.cxnetwork.com/artificial-intelligence/articles/why-your-predictive-analytics-and-ai-projects-are-failing-and-how-to-transform-your-success
2. US Food and Drug Administration. "Artificial Intelligence in Drug Manufacturing." 2023. https://www.fda.gov/media/165743/download?attachment
3. US Food and Drug Administration. "Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products - Discussion Paper and Request for Feedback." May 2023. https://www.fda.gov/media/167973/download?attachment
4. European Medicines Agency. "Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle." 11 September 2024. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-use-artificial-intelligence-ai-medicinal-product-lifecycle_en.pdf
5. European Medicines Agency. "Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle – Draft." 13 July 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/draft-reflection-paper-use-artificial-intelligence-ai-medicinal-product-lifecycle_en.pdf
6. US Food and Drug Administration. "Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products Draft Guidance." January 2025. https://www.fda.gov/media/184830/download
7. US Food and Drug Administration. "Artificial Intelligence-Enabled Device Software Functions: Lifecycle Management and Marketing Submission Recommendations Draft Guidance." 7 January 2025. https://www.fda.gov/media/184856/download
8. International Society for Pharmaceutical Engineering. *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition).* North Bethesda, MD: International Society for Pharmaceutical Engineering. July 2022.
9. International Society for Pharmaceutical Engineering. *ISPE GAMP® Guide: Records and Data Integrity.* North Bethesda, MD: International Society for Pharmaceutical Engineering. March 2017.
10. International Society for Pharmaceutical Engineering. *ISPE GAMP® RDI Good Practice Guide: Data Integrity by Design*. North Bethesda, MD: International Society for Pharmaceutical Engineering. October 2020.
11. International Organization for Standardization. "ISO/IEC 42001: 2023 Information technology – Artificial Intelligence – Management System." December 2023. https://www.iso.org/standard/42001

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Brandi Stockton, MBA, Founder and CEO of The Triality Group, has over 25 years of pharmaceutical industry experience across several areas of GxP with a specialization in computer systems quality and data integrity. Brandi joined ISPE in 2014, currently serving as Chair of GAMP Americas, co-lead of the GAMP Global Software Automation and AI Special Interest Group, and as a member of the AI CoP Steering Committee. She was the visionary originator and principial strategist of the AI Guide initiative.

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Martin Heitmann, Consultant with The Triality Group, advises life science organizations on advancing their capabilities in data, digital solutions, and quality management with a strategic focus on innovation and transformation. Leveraging expertise from his degrees in mathematics, he drives progress and inspires excellence in the life sciences. An ISPE member since 2022, he has contributed to numerous publications and various guides, currently serves as Secretary of the GAMP Global Software Automation and AI Special Interest Group, is a member of the GAMP D/A/CH Steering Committee, and was a co-lead of the AI Guide initiative.

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MOBILE MANUFACTURING IN PHARMA
Promise, Progress, and Practicalities

By Mark Buswell, PhD, Andrew Dell, Celeste Frankenfeld Lamm, PhD, Michael K. O'Brien, PhD, and Dennis Powers

Advancements in technology—such as process intensification, continuous manufacturing, and 3D printing—are enabling transportable and point-of-care (PoC) medicines manufacturing, especially with the rise of personalized medicine. Modular, small-scale production systems are particularly well-suited for cell and gene therapies and other advanced therapy medicinal products (ATMPs) designed for patient-specific treatments.

Even for small molecule oral solid dose medicines, supply chain constraints and access considerations may make modular and transportable production units a viable option. However, regulatory challenges persist—particularly in terms of demonstrating product comparability across modular units. Additionally, scaling innovative modular manufacturing remains difficult.

While technological advancements have significantly progressed, commercial adoption of transportable and point-of-care manufacturing remains limited, primarily due to persistent regulatory and economic barriers.

INTRODUCTION

The ISPE PQLI® Transportable Point-of-Care Manufacturing Technology Team has defined transportable or point-of-care manufacturing as: "a capability that can be readily deployed temporarily in closer proximity to the patient base" [1]. Expanding on this, transportable or point-of-care (PoC) medicines manufacturing refers to the concept of highly mobile manufacturing units that can be relocated within or across different locations, including geographies and regions. In the full extension of the concept, these units can even be deployed directly at the point-of-care, such as in a clinical or hospital setting. This approach naturally implies a diseconomy of scale while supporting greater patient segmentation, ultimately leading to customized medicines tailored to individual patients.

Several factors have driven this concept, including regulatory requirements to keep the latter stages of medicines manufacturing within a region, supply chain demands for responsiveness to unforeseen needs, the flexibility to leverage lower cost manufacturing regions, and the need to improve access to medicines in underserved poorer countries.

Coupled with these macro socio-economic drivers, technological advancements have made highly mobile manufacturing units a viable option. These include advances in process intensification—such as continuous manufacturing for both drug substance and drug product—as well as alternative formulation approaches, including 3-D printing of drug product [2].

Additionally, the rise of combination products and the ability to co-formulate specific combinations tailored to patient needs make transportable modular manufacturing a potentially more attractive option.

Finally, the emergence of novel modalities—such as cell and gene therapies—custom biologics and more recently, mRNA-based vaccines—has disrupted the traditional global manufacturing hub model.

This paper aims to review the current status and trends in transportable and point-of-care medicines manufacturing. It will reassess the key drivers behind the concept, examine industry progress in deploying this approach for both clinical and commercial manufacturing, and identify areas where the ideas remain largely theoretical. Additionally, it will explore how the regulatory environment is evolving to accommodate these advancements. Finally, we will consider potential future developments and their timelines, acknowledging the inherent uncertainties in making predictions.

Because there are varying transportable approaches to consider for future manufacturing platforms (eg. mobile truck/trailer, prefabricated modules, portable units), and there is no one size fits all solutions to accommodate varying manufacturing processes, the paper will not focus on the transportation aspect itself.

DRIVERS FOR TRANSPORTABLE AND POINT-OF-CARE MANUFACTURING

Drivers of transportable and point-of-care manufacturing vary by modality and whether it pertains to primary drug substance or secondary drug product manufacturing.

For small molecules, large molecule biopharmaceutics and protein-based antigen vaccines, drug substance manufacturing typically benefits from the economies of scale achieved through centralized high-volume production. While the COVID-19 pandemic and recent geopolitical uncertainties have tempered this to some degree, the response has largely been a shift toward re-shoring or regionalizing primary drug substance manufacturing to enhance supply chain security. However, even with regionalized production, drug substance manufacturing for these modalities remains centralized and a long way from being truly transportable or suitable for point-of-care deployment.

For secondary drug product manufacturing, in addition to supply security concerns, financial considerations and access to medicines also play a role in driving some companies to regionalize or localize drug product manufacturing. Certain countries, such as Brazil, are working to implement fiscal and regulatory policies that incentivize local drug product manufacturing. This typically begins with final-stage packaging but has the potential to expand further upstream as governments leverage medicine regulations to stimulate economic growth.

Additionally, some global pharmaceutical companies have embraced an access-to-medicines agenda aiming to deploy drug product manufacturing solutions into developing countries. This gave rise to the development of "factory-in-a-box" concepts, most notably by GSK in partnership with Bryden Wood [3]. This concept was developed as part of GSK's Africa 2020 strategy—an initiative that focused on designing a modular factory facility that was partially pre-assembled offsite and could be deployed and validated rapidly in challenging markets.

Another example of industry innovation in response to these challenges was the collaboration between Pfizer, GSK, GEA, and G-CON to develop a Portable Continuous Modular Manufacturing (PCMM) unit based on continuous direct compression tableting technology to enhance production flexibility and efficiency [4].

Over the past decade, there has been a significant emergence of new modalities including cell and gene therapies (also known as ATMPs, mRNA, and custom biologics). The emerging modalities are generally more suited to transportable and point-of-care manufacturing than traditional modalities, as they tend to be more patient-specific and produced in significantly lower volumes. Additionally, these new modalities often have challenging storage and transportation requirements, making centralized manufacturing and distribution via traditional pharmaceutical supply chains more difficult. A notable example was the Pfizer-BioNTech mRNA COVID-19 vaccine, which required -90°C to -60°C transit and storage conditions. While this posed logistical challenges even in developed markets, it created significant obstacles in regions lacking advanced cold chain distribution infrastructure.

TECHNOLOGICAL ADVANCES AND NEW MODALITIES

Historically, industrialized pharmaceutical manufacturing has relied on large, fixed factory installations that serve as global or regional supply hubs. To ensure supply, pharmaceutical companies typically maintain multiple production sites for revenue-generating or medically essential medicines. The dominant production model in these facilities—for both drug substance and drug product—has traditionally been batch manufacturing, and this remains largely the case today. However, technological advancements, cost pressures, and evolving quality and regulatory expectations have driven innovation in manufacturing operations.

Continuous Manufacturing

One such innovation is the gradual adoption of continuous manufacturing for both drug substances and drug products. This shift inherently leads to significant process intensification with a correspondingly much smaller physical footprint while maintaining the same product output. Implementing this approach allows drug manufacturers to achieve the necessary production capacity within a considerably smaller facility compared to traditional batch operations. This paradigm shift will be a critical factor driving the deployment of a decentralized or point-of-care manufacturing network.

Small Molecule Pharmaceuticals

Drug product manufacturing has also been shifting toward continuous operations. In oral solid dose (OSD) manufacturing, tableting is already a continuous process. However, operations such as wet granulation and drug powder blending have historically been batch processes. Recent advances with twin screw wet granulations systems, continuous driers and powder blending technologies now make fully continuous oral solid dose manufacturing possible [5].

Similar to drug substance manufacturing, continuous OSD technologies require significantly smaller physical footprints, making modular manufacturing units a more viable option. For example, GSK reported that the physical footprint of their drug substance manufacturing operations was reduced thereby improving capacity and reducing costs [6]. This reduction not only leads to significant savings in initial capital investment and ongoing operating costs but also enables the design of modular skids for drug substance synthesis that can be constructed offsite, shipped, and reassembled as needed, enabling a portable manufacturing paradigm.

However, widespread adoption of continuous manufacturing for drug substances is still constrained by the limitations of certain chemical transformations required to achieve the completed synthesis of the desired active ingredient. Not all chemical reactions are compatible with flow chemistry, but these challenges can be managed through mini-batch or fed-batch approaches.

Large Molecule Biologics

Continuous manufacturing is particularly valuable in biologics and can drive efficiency in production, which in turn can reduce the costs of biomanufacturing and provide more people with access to such therapies [7]. The development of transportable or modular facilities for manufacturing custom biologics is also advancing, driven by the need for flexibility, scalability, and speed. These

facilities, which rely on continuous and connected intensified processes, offer significant advantages— particularly in regions where traditional large-scale manufacturing is not viable.

Due to their smaller footprints and modular design, these platforms are inherently deployable and scalable, reducing time to market and capital expenditure for biologics manufacturers. They can be assembled more quickly than conventional facilities and are adaptable enough to accommodate various stages of biologics production, including both upstream and downstream processes. Additionally, they support the use of single-use technologies, which help to minimize contamination risks and are especially beneficial for smaller batches, such as those required for personalized medicines [8].

For those process steps, such as purification, which require significant volumes of buffer, strategies will need to be developed for local or regionalized buffer production—leveraging technologies such as in line dilution or through innovative supplier arrangements.

While continuous manufacturing of biologics has not yet reached the level of advancement seen in small molecule pharmaceuticals, significant investment and technological progress are driving its development. Many leading process technology providers continue to innovate, launching systems and platforms designed for intensified and continuous biologics manufacturing. In addition to larger biotech companies, a growing number of universities and start-up companies are focused on developing continuous platforms to enhance traditional mammalian and microbial-based processes as well as pioneering novel approaches for manufacturing mRNA vaccines and therapies.

Advanced Therapy Medicinal Products

Advanced therapy medicinal products (ATMPs) are particularly well-suited for point-of-care manufacturing. These therapies—which involve techniques such as gene editing, cell manipulation and tissue engineering—generally require immediate delivery to patients, making hospital-based manufacturing highly desirable. Currently, production is managed under regulatory exemptions granted by various authorities. However, as ATMPs become more widespread, new regulatory frameworks will likely need to emerge to better support point-of-care manufacturing.

One evolving concept in this area is point-of-care manufacturing readiness [9]. This framework outlines three key aspects of PoC manufacturing readiness: institutional procedures and staff training; material infrastructure and equipment; and relationships with providers and distributors. This concept has merit, given the need for drug manufacturers and healthcare providers to integrate their quality and operational management systems in an effective and efficient manner, ensuring the quality of the product and the health and safety of the patients.

As with any cGMP manufacturing site, the training of operators and staff within a PoC operation will be critical to ensure compliance with quality systems and regulatory licenses and authorizations. Standardization of procedures and systems across PoC sites, minimizing manual tasks through automation, and implementation of digital technologies wherever possible, will be critical to mitigate the risk of quality issues and deviations.

Autologous Therapies

Autologous cell therapies are a form of personalized medicine in which a patient's own cells are extracted, modified through a proprietary process, and then reintroduced for therapeutic use. Among these, CAR T cell therapies—an immunotherapy that enables the patient's immune system recognize and attack cancer cells—have gained significant attention over the past decade. As of June 2025, six US Food and Drug Administration (FDA)-approved CAR T therapies are on the market; however, several challenges remain. The centralized manufacturing model for CAR T therapies has, at least in part, been identified as a major supply chain bottleneck limiting patient access in the US [10].

Shifting toward distributed or point-of-care manufacturing could enhance capacity, streamline logistics, and reduce lead times. This approach could help mitigate risks associated with chain of custody, cold transport and storage, and the short treatment window following initial apheresis cell collection. In this context, manufacturing could be performed very close to where the patients are treated—e.g., in hospitals and clinics. Localized "production units" could be designed for mobility allowing for transport to different locations where patients require treatment.

However, this model presents its own set of unique quality and regulatory challenges, as it diverges from traditional and accepted drug manufacturing standards. For example, quality control (QC) testing requirements for cell therapies can be significant and will need to be addressed as a potential component of the localized facility if existing capability is not in close proximity. Despite these hurdles, the strongest driver for transportable and point-of-care medicines manufacturing will likely be the increasing demand for customized, patient-specific therapies like CAR T cell treatments.

Pharmacy Compounding and Formulation

Industry consolidation, drug shortages, and the increasing demand for customized drug products—such as co-formulations and patient-specific dosages—are driving innovation and investment in the capacity of both hospital-based and independent 503A and 503B compounding pharmacies. Consolidation has largely been fueled by heightened regulatory scrutiny and oversight following quality lapses, some of which have had serious consequences, including patient fatalities [11]. Companies that have remained in operation have focused on improving their processes and quality systems while attempting to increase their capacity to address the current drug shortage issues. Additionally, hospitals are exploring innovative solutions from companies like OnDemand Pharma (ODP), which offers transportable compounding pharmacy units that can be temporarily located at their site to compound the most critical drugs in shortage. ODP and other companies are developing new processes and technology platforms to support a distributed

manufacturing network, further enhancing the resilience and flexibility of pharmaceutical supply chains.

3D Printing

A significant advancement in oral solid dose formulations is the use of 3D printing. This takes various forms. One example is GSK's Liquid Dispensing Technology (LDT), which deposits a solution of the active ingredient onto a placebo tablet. This fully continuous process can be scaled up to produce two million tablets per day from a single modular, self-contained unit [12]. In 2016 Aprecia Pharmaceuticals became the first company to receive FDA approval for 3D-printed tablets, Spritam (levetiracetam) for the treatment of epilepsy [13]. 3D printing holds promise for personalized medicine, potentially enabling drug formulation in pharmacies, at home, or even at the patient's bedside. One of the leading innovators in the field is FabRx, which offers a range of 3D printing solutions employing a variety of techniques with a strong focus on developing the technologies for personalized medicines applications.

MODULAR MANUFACTURING FACILITIES

Modular manufacturing is the process of assembling individual prefabricated sub-assemblies in a controlled factory setting to create a substantially complete building product ready for transportation to a host site. In pharmaceutical and biopharmaceutical applications, over 85% of the assembly is completed in the factory, while the remaining work is completed at the host site. The approach is based on Design for Assembly (DfA) principles and practices.

Modular prefabricated facilities can vary in size, ranging from small 500 square-foot units to much larger multi-story structures. For distributed or point-of-care manufacturing, most facilities are expected to fall within the 500 to 5,000 square-foot range, depending on factors such as process requirements, output capacity, and the need for relocation. Installation locations can also vary, with some requiring the facilities to be housed within a shell structure, such as a warehouse, while others may be placed outdoors, such as in a parking lot adjacent to a hospital or treatment center.

For manufacturers deploying modular facilities across multiple sites, a standardized pre-engineered platform approach is preferred. This ensures that facilities can be easily replicated, yet also configurable to accommodate site-specific requirements or constraints. This approach can significantly reduce the time required to deliver a new facility and reduce the total cost of ownership of the manufacturer's network.

Successful Modular Manufacturing Models

Core elements of these models include:

- Factory assemblies follow a process flow moving efficiently through the factory footprint from beginning to end, utilizing factory standard operating procedures (SOPs) to organize and streamline each step of the build.
- Modules are designed and built on a structural product platform that supports both the factory environment and transportation.
- Build process primarily relies on pre-engineered sub-components and assemblies that are well-established and familiar to the assembly team.
- The majority of sub-assemblies (*i.e.*, structural, architectural, process, HVAC, etc.) are constructed just-in-time (JIT) in parallel, reducing overall project duration.
- Design details are coordinated using a collaborative 3D Building Information Modeling (BIM) system.
- Design that is compliant with all regulatory and code requirements based on the installed location.

The Modular Build Process in Four Phases

1. Scope of Delivery Development and Approval

This phase involves defining the design basis and contractually agreeing on the scope, schedule, and cost of the manufacturing module. Depending on the level of complexity, this step can take anywhere from a few days to several months. Modular fabrication does require a higher degree of front-loaded information to enable rapid delivery. The phase is completed once sufficient funds are approved to procure materials and allocate factory capacity to the project. By the end of this phase, all required materials and personnel resources are identified, and planning has been initiated.

2. Fabrication and Assembly

Design details necessary for fabrication and assembly are finalized while externally sourced materials arrive and undergo inspection in parallel. The fabrication and assembly process follows a predetermined sequence through the factory, ensuring each step of the build is prescheduled and completed in a controlled environment using standardized processes and materials. The buildout includes all rough-in scope and all final finishes, covering structural, architectural, mechanical, electrical and building management systems—down to lighting outlets, HVAC grills, hand wash sinks, and even door hardware. Quality control is critical, with each system undergoing rigorous documented inspections to ensure compliance with building codes and design specifications. Finally, inspection and approval are documented with an approved documented Factory Acceptance Test (FAT).

3. Packaging and Transportation

Once fabrication and assembly are completed, modules are packaged and transported to the site. Depending on the size and distance, transportation methods may include trucking, rail, or shipping.

4. Installation and Site Acceptance Testing

The final phase takes place at the host site and includes rigging, site connections, and Site Acceptance Testing (SAT). Rigging involves lifting modules off transport vehicles using cranes and then moving them into position. For multi-module setups, the units are secured together using fasteners or welding, and plumbing, electrical, and HVAC connections are completed, often using pre-installed channels within the modules. Modules are then

integrated into the host site's utilities and monitoring systems. The process concludes with an SAT to verify all systems are fully operational and meet the user's performance requirements.

Overall, modular facilities offer a streamlined and efficient alternative to traditional construction methods, providing advantages in speed, cost, quality, and sustainability.

REGULATORY AND QUALITY CONSIDERATIONS

When pursuing transportable, decentralized, or point-of-care manufacturing, regulatory and quality considerations are centered around the following key areas.

Defining a Manufacturing Site

Current regulations and guidelines were designed for traditional fixed-location, large-scale manufacturing facilities that require a specific geographic address to be registered. However, this requirement may be impractical, and not commensurate with the risk when dealing with mobile manufacturing units or networks of interconnected facilities. For installations of multiple yet similar manufacturing units, the listing of each address neglects the important relationships and interdependencies between the units.

Applying Quality Systems Across Sites

Traditional manufacturing sites have dedicated personnel responsible for quality oversight and management ensuring a strong quality culture. However, applying this level of oversight becomes more complex when dealing with mobile manufacturing units or multiple interconnected units spread across different locations. Additionally, maintaining connectivity across the related units is essential for managing quality events such as deviations, investigations, and change management effectively. Leveraging IoT (Internet of Things), digital tools and technology platforms can help to address these challenges.

Demonstrating Comparability

Traditionally, product comparability across manufacturing sites has been demonstrated through bioequivalence studies, process performance qualification (PPQ), and long-term stability studies to establish product equivalence. However, these approaches can significantly delay the implementation of a new site and become impractical (for both application and review) when deploying a large number of highly similar manufacturing units. Standardization across decentralized sites can reduce the risk of product non-equivalence, but questions remain: What level of evidence is necessary to demonstrate equivalence? How should it be maintained over time? How should it be reported to regulatory authorities?

Conducting Inspections

A portable manufacturing unit may transition between different inspectional jurisdictions, and multiple decentralized sites may span across regulatory boundaries. In each case, the question arises: Who holds the authority to ensure compliance with Good Manufacturing Practices (GMPs)?

Three major regulatory agencies—UK's Medicines and Healthcare products Regulatory Agency (MHRA), FDA, and European Medicines Agency (EMA)— have engaged the public to better understand the regulatory needs and challenges in transportable, decentralized, and point-of-care (PoC) manufacturing. Their focus has been on identifying barriers to implementation and proposed solutions. Following public consultations, each agency is working to adapt legislation and guidelines to accommodate decentralized manufacturing models.

- The MHRA shared the results of their public consultation in 2023 (14) and new regulations were established, coming into effect 23 July 2025 (15).
- The FDA shared the feedback they received from their discussion paper and public workshop in a 2023 report. Its action plan included developing guidance as appropriate, and coordinating with international regulatory agencies (16).
- The EMA's Quality Innovation Group held a Listen and Learn Focus Group meeting in 2023, gathering industry input. Its final report included an action item to develop appropriate guidance for decentralized manufacturing adoption (17).
- Additionally, the EU's draft pharmaceutical legislation amendment incorporates the concept of decentralized manufacturing (18).

Though formal regulatory expectations are still in development, public engagement has revealed several common themes:

- Industry and patient groups strongly support regulatory efforts to ensure a clear path forward for decentralized manufacturing (DM) and PoC manufacturing.
- Preliminary definitions of what constitutes PoC have varied somewhat, but agencies have indicated that they will refine these based on industry feedback.
- Sentiment has coalesced around the need for a centralized Pharmaceutical Quality System (PQS) to manage quality across geographic locations.
- The concept of a centralized hub responsible for quality oversight of DM locations is gaining support.

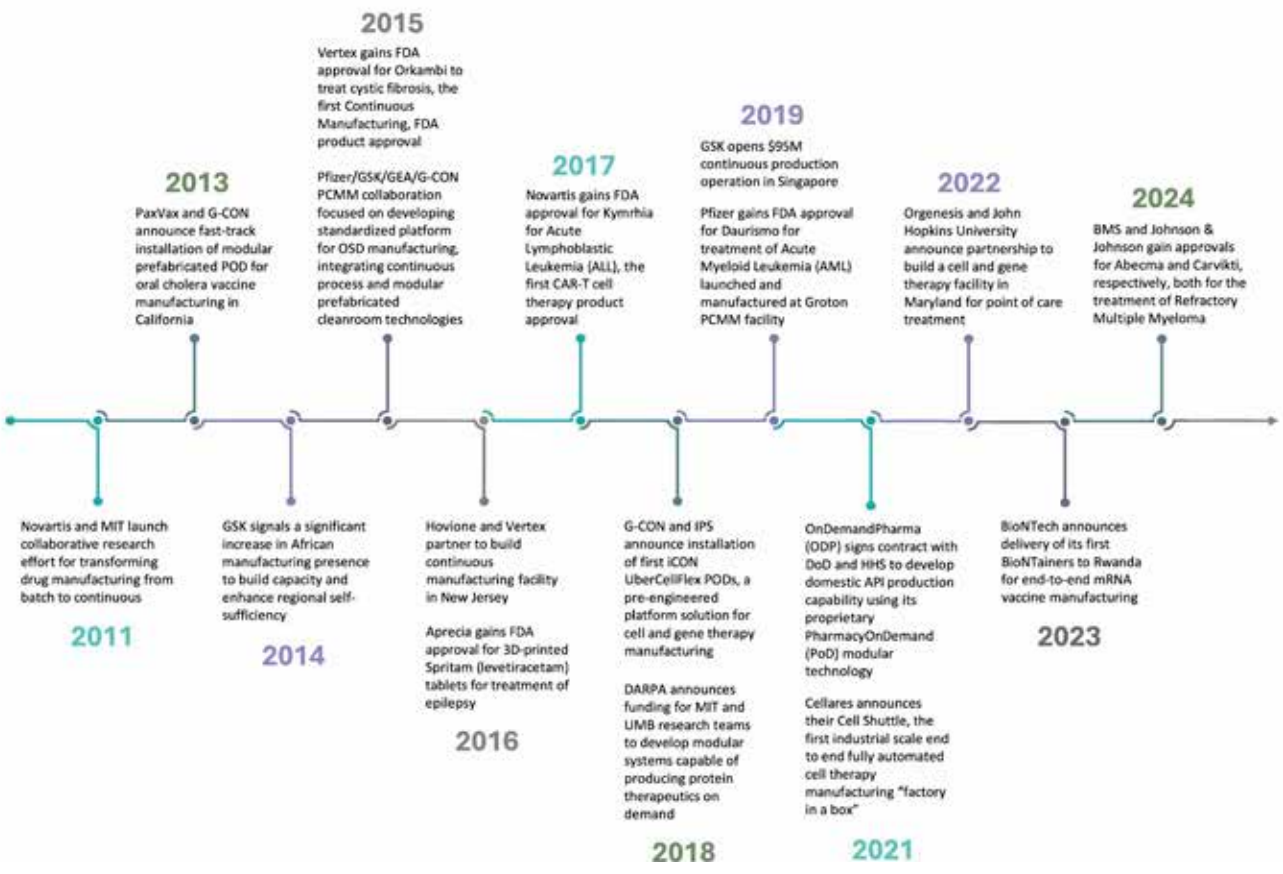
Proposed Regulatory Approaches

- The MHRA suggests implementing a master file to document quality oversight and serve as a comparability reference.
- The FDA has proposed risk-based assessments and regulatory tools such as Post-Approval Change Management Protocols (PACMP, see ICH Q12) to gain upfront agreement regarding testing and acceptance criteria for new or relocated sites.
- To ease resource strain from multiple DM or PoC sites, regulators favor a risk-based approach, prioritizing oversight at the central hub and streamlining it at distributed sites.

Decentralized Manufacturing: Regulatory Focus

1. Current regulations require specific geographic manufacturing location in regulatory submissions, and any site change requires

Figure 1: Timeline of specific transportable and point-of-care manufacturing initiatives.



notification, pre-approval inspection (PAI) etc.
2. Existing regulations are designed for a centralized quality system, which may need adaptation for decentralized models.
3. Validation of equipment and processes remains a core requirement, particularly for ensuring comparability and regulatory acceptance across multiple sites.

INDUSTRY PROGRESS OVER THE LAST DECADE

Over the past decade, investments in innovation and technology have accelerated the development of process and facility platforms, laying a strong foundation for transportable and point-of-care manufacturing. Advances in process intensification, single-use technologies, and continuous manufacturing—alongside progress in personalized medicines and therapeutics—have significantly reduced process footprints compared to traditional centralized models.

Smaller process footprints, along with reduced utility and operational demands, have enabled the development of transportable, rapidly deployable modular manufacturing platforms. As a result, several companies are now integrating advanced process, automation, and modular technologies to support decentralized and point-of-care manufacturing models.

Several vendors offer software solutions for real-time production management through process automation and control systems, data management and analytics, Industrial Internet of Things (IIoT) and digital twins to enhance efficiency. Some key vendors are AVEVA, Siemens, Rockwell Automation, Emerson, and SAP.

Despite technological progress in transportable and point-of-care manufacturing, commercial adoption remains limited. Most medicines and vaccines are still produced in centralized facilities due to challenges in ensuring consistent quality, navigating regulations, and lacking strong economic incentives [19].

DIGITAL IT PLATFORMS FOR TRANSPORTABLE AND POC MANUFACTURING

Although digital IT platforms play a crucial role in enabling and managing any manufacturing system, their importance is amplified with transportable and point-of-care medicines manufacturing operations. Digital IT platforms provide essential tools for monitoring, controlling, optimizing, and ensuring the quality of manufacturing processes. The unique challenges of decentralized manufacturing make the adoption of a variety of digital solutions essential to the success of this paradigm.

Cloud-Based Manufacturing IoT Platforms

By their very nature, modular transportable manufacturing systems will have a significant dependency on cloud-based manufacturing IoT platforms to remotely monitor and control

production processes. Commercial cloud solutions are available that support digital twins, supply chain management, and AI-driven process optimization—particularly for flexible, point-of-care drug production environments. Examples include Siemens Digital Industries, Microsoft Azure for Manufacturing, and Amazon Web Services (AWS) IoT. Some cloud services allow secure data storage and process control, critical for managing mobile and transportable manufacturing units, while others provide a suite of IoT tools that can support real-time monitoring, data analytics, and cloud-based control of transportable and point-of-care production facilities. These systems enable manufacturers to remotely manage decentralized production units and ensure compliance with regulatory standards.

MANUFACTURING EXECUTION AND ELECTRONIC BATCH RECORDS

Pharma Manufacturing Execution Systems (MES) are well established in traditional biopharmaceutical manufacturing, and there are several well-established technology providers (e.g. Siemens Opcenter, Emerson Syncade and Rockwell Automation PharmaSuite, among others). These systems can be adopted for decentralized transportable production units, offering real-time control and coordination of unit functionality by integrating automation, materials management and product optimization. For decentralized manufacturing, MES is essential for maintaining high compliance standards and traceability. Most MES platforms include electronic batch record functionality, which supports regulatory requirements for these applications.

AI AND PREDICTIVE ANALYTICS PLATFORMS

AI and predictive analytics platforms can be integrated with manufacturing systems to optimize production processes, predict failures, and manage quality control. These tools are valuable for providing insights into machine performance, ensuring product consistency, and avoiding downtime.

BLOCKCHAIN FOR SUPPLY CHAIN AND QUALITY CONTROL

With decentralized manufacturing, transparency, traceability and data security across a network of decentralized production systems are critical. Blockchain potentially provides a solution to these challenges. For example, Hyperledger Fabric (IBM Blockchain) can track everything from raw materials to final product, ensuring that decentralized, PoC manufacturing is compliant with regulatory standards and traceable throughout the supply chain.

Another example is Chronicled, a pharmaceutical blockchain-based platform that helps track medicines in real time, ensuring that portable or PoC manufacturing units adhere to regulatory requirements. These types of blockchain systems offer immutable records of production, enhancing safety and regulatory compliance.

DIGITAL TWINS AND AUGMENTED REALITY PLATFORMS

Digital twin technologies enable the creation of virtual replicas of pharmaceutical manufacturing processes, allowing for real-time monitoring, simulation, and optimization of decentralized manufacturing units. These models help predict system performance, enabling point-of-care units to adapt quickly to changes in demand or operating conditions.

Augmented reality (AR) platforms are already used in traditional manufacturing for operator training, remote inspections, and maintenance—a trend accelerated by the COVID-19 pandemic. In transportable and PoC manufacturing, AR will help local teams troubleshoot, maintain systems, and optimize processes. Other digital platforms—Quality Management Systems, Supply Chain Management, and Manufacturing Collaboration tools—will be crucial in ensuring efficiency, compliance, and coordination.

WHAT'S NEXT AND WHEN?

Looking ahead, continued investment in research and development, regulatory harmonization, and infrastructure development will be essential to advancing transportable and PoC manufacturing technologies. These innovations have the potential to transform how medicines are produced and distributed, improving access to essential treatments and addressing global health disparities.

The greatest momentum is expected in ATMP manufacturing, where the drivers for adoption are most compelling, and regulators seem most interested in providing a conducive regulatory framework to facilitate access to ATMP treatments. Economies of scale will likely continue to favor centralized manufacturing for traditional modalities. Regional manufacturing may emerge in response to supply chain security or regional economic incentives, rather than a fundamental shift in production models.

One potential exception is the use of 3D printing for oral solid dose medications. While there is significant academic interest in this technology, and some products have received regulatory approval and achieved market access, it remains uncertain whether the clinical and economic benefits will be strong enough to drive widespread adoption.

CONCLUSIONS

Several industry and socio-economic factors are driving the need to advance transportable and POC manufacturing at a commercial scale. Personalized medicine and ATMPs, currently face significant manufacturing and logistical challenges, which could potentially be mitigated through the implementation of a point-of-care (PoC) model—ultimately reducing the cost of care and improving patient outcomes.

The process and facility technology platforms required to implement this model already exist and have proven to be effective for both clinical and commercial manufacturing operations. Digital platforms, cloud-based services, and IIoT technologies have matured and have been successfully deployed across various industries. By integrating the right combination of these solutions, drug manufacturers can now build scalable PoC platforms.

However, the most significant barriers to implementation stem from the need for harmonized regulatory guidance regarding the adaptation of traditional regulatory systems, which were designed for centralized drug manufacturing and distribution

model. Regulatory bodies in the United States and Europe have begun engaging with industry and drafting preliminary guidance. Despite this progress, clear regulatory pathways for the commercial adoption of transportable and PoC manufacturing remain a work in progress, requiring continued effort to define and establish.

References

1. ISPE PQLI® Transportable/Point of Care Manufacturing Team. "Transportable Manufacturing." *Pharmaceutical Engineering*. 13 September 2021. https://ispe.org/pharmaceutical-engineering/ispeak/transportable-manufacturing
2. Wang S, Chen X, Han X, et al. "A Review of 3D Printing Technology in Pharmaceutics: Technology and Applications, Now and Future." *Pharmaceutics*. 26 January 2023. https://doi.org/10.3390/pharmaceutics15020416
3. Bryden Wood. "GlaxoSmithKline 'Beta' Building Prototype." Accessed 9 April 2025. https://www.brydenwood.com/projects/glaxosmithkline-beta-building-prototype/s1317/
4. Palmer, E. "Pfizer and GSK to work together on continuous manufacturing." *Fierce Pharma*. 29 October 2015. https://www.fiercepharma.com/manufacturing/pfizer-and-gsk-to-work-together-on-continuous-manufacturing
5. Arshad MS, Zafar S, Yousef B, et al."A Review of Emerging Technologies Enabling Improved Solid Oral Dosage Form Manufacturing and Processing." *Advanced Drug Delivery Reviews*. November 2021. https://doi.org/10.1016/j.addr.2021.113840
6. Palmer, Eric. "GSK Opens $95m Continuous Production Operation in Singapore." *Fierce Pharma*. 8 July 2019. https://www.fiercepharma.com/manufacturing/gsk-opens-130m-continuous-production-facilities-singapore
7. Scott C, Gadgil H, Abbott J. "Process Intensification, Driving Efficiencies Across the Spectrum of Biomanufacturing." *BioProcess International eBooks*. April 2024. https://www.bioprocessintl.com/sponsored-content/ebook-process-intensification-driving-efficiencies-across-the-spectrum-of-biomanufacturing
8. Chen R, Hwang C, Lee K, Zydney A, Kokai-Kun JF. "Where Do We Stand on Adopting Continuous Manufacturing for Biologics?" *BioProcess Online*. 5 December 2022 https://www.bioprocessonline.com/doc/where-do-we-stand-on-adopting-continuous-manufacturing-for-biologics-0001
9. Bicudo E, Brass I. "Institutional and Infrastructure Challenges for Hospitals Producing Advanced Therapies in the UK: The Concept of 'Point-Of-Care Manufacturing Readiness'." *Regenerative Medicine*. 06 September 2022. https://doi.org/10.2217/rme-2022-0064
10. Elsallab M, Maus MV. "Expanding access to CAR T cell therapies through local manufacturing." *Nature Biotechnology*. 26 October 2023. https://www.nature.com/articles/s41587-023-01981-8
11. Guharoy N, Novlasky J, Haydar A, Fakih M, Harman R. "Compounding Pharmacy Condundrum." *CHEST Journal*. Volume 143, Issue 4, p896-900. April 2013. https://journal.chestnet.org/article/S0012-3692(13)60197-X/fulltext
12. GSK. "Liquid Dispensing Technology (LDT)." Accessed April 9, 2025. https://www.gsk.com/media/2758/liquid-dispensing-technology-leaflet.pdf
13. Aprecia. "FDA Approves the First 3D Printed Drug Product." 3 August 2015. Accessed 9 April 2025. https://aprecia.com/resources/press/fda-approves-the-first-3d-printed-drug-product/
14. UK Government. Medicines & Healthcare products Regulatory Agency. "Consultation on Point-of-Care Manufacturing." 25 January 2023. Accessed 9 April 2025. https://www.gov.uk/government/consultations/point-of-care-consultation/consultation-on-point-of-care-manufacturing
15. UK Government. Medicines & Healthcare products Regulatory Agency. "Decentralised Manufacture Hub." 19 March 2025. Accessed 9 April 2025. https://www.gov.uk/government/collections/decentralised-manufacture-hub
16. US Food and Drug Administration (FDA). Center for Drug Evaluation and Research "Distributed Manufacturing of Drugs: Stakeholder Feedback and Action Plan." November 2023. Accessed 9 April 2025. https://www.fda.gov/media/173449/download
17. European Medicines Agency. "First listen-and-learn focus group meeting of the Quality Innovation Group." 13 March 2023. Accessed 9 April 2025. https://health.ec.europa.eu/medicinal-products/legal-framework-governing-medicinal-products-human-use-eu/reform-eu-pharmaceutical-legislation_en
18. European Commission. Directorate-General for Health and Food Safety. "Reform of the EU Pharmaceutical Legislation." 26 April 2023. Accessed 9 April 2025. https://health.ec.europa.eu/medicinal-products/legal-frameworkk-governing-medicinal-products-human-use-eu/reform-eu-pharmaceutical-legislation_en
19. Markarian J. "Considering the Promises of Point-of-Care-Manufacturing." *PharmTech.com*. 2 November 2023. Accessed 9 April 2025. https://www.pharmtech.com/view/considering-the-promises-of-point-of-care-manufacturing

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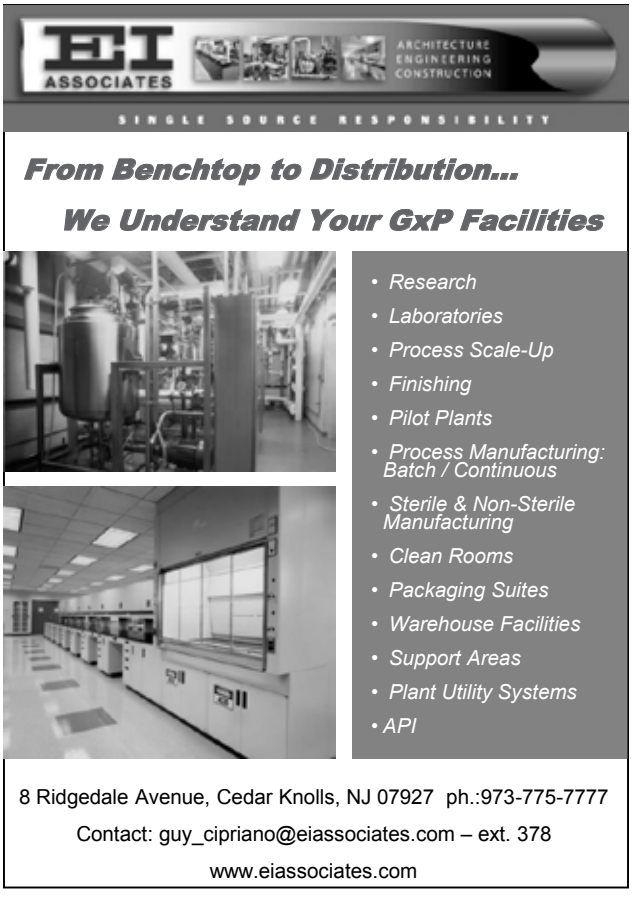

STREAMLINING POST-APPROVAL CHANGES
Industry Insights on ICH Q14

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Simplified approaches that enable changes to analytical procedures over their lifecycle are needed to allow continual improvements and adaptations due to technological obsolescence and other challenges. This article reflects on the positive impact that the recent ICH Q14 guidance can have on facilitating these changes. Five examples are provided that are based on scenarios in which analytical procedure changes were required and show what these would look like in a future state where recent guidance is fully implemented. The examples illustrate the potential of ICH Q14 concepts to facilitate post-approval changes to analytical procedures, ultimately benefiting patients through improved assurance of product quality and regulatory efficiency.

INTRODUCTION

The recently finalized ICH Q14 guideline outlines science- and risk-based approaches for developing and maintaining analytical procedures [1]. It also provides guidance on the change management of these procedures, using principles described in ICH Q12, which was finalized by ICH in late 2019 to facilitate post-approval changes for pharmaceutical products but has faced limited implementation due to the lack of regulatory harmonization and acceptance [2].

The analytical procedures in today's Quality Control (QC) lab, some of which were developed two or more decades ago, generally lag behind the advances in the field of instrumentation, sample preparation tools, and data processing. This is primarily because changing analytical procedures is expensive, time-consuming, and can pose challenges in implementation while maintaining regulatory compliance, given the variety of expectations from regulatory authorities and the complexity of global supply chains [3]. In a recent article authors from one major pharmaceutical company note that out of 6,000 changes for different commercial products, 55% were categorized as regulatory-relevant; these changes necessitated the submission of almost 90,000 variations to different countries. Of these, 43% (approximately 38,700) were related to analytical procedures [4].

To ensure that analytical procedures remain fit for purpose, they must accommodate product and process changes while incorporating the advances in analytical technology, instrumentation, and scientific knowledge that occur over time. Furthermore, as the molecular complexity of drugs increases, we anticipate the evaluation of their critical quality attributes (CQAs) to utilize more complex analytical procedures and instrumentation that are even more likely to require changes during the lifecycle of the drug. The ICH Q14 guideline emphasizes the need for continual improvement of analytical procedures, from smaller modifications to the complete replacement of outdated methods with new technologies. Changes in performance characteristics or additional information on analytical attributes to be tested may necessitate the revision of the Analytical Target Profile (ATP) or the adoption of a new procedure.

A frequent scenario in modern QC labs involves upgrading to state-of-the-art instrumentation and/or techniques to replace an obsolete one, which often requires a time-consuming and complex specification update because existing specification criteria are no longer appropriate for the newer, more sensitive methods. The shared goal of sponsors and regulators is to ensure that the updated analytical procedures continue to provide accurate, precise, and specific measurements of quality attributes.

ICH Q14 CHANGE MANAGEMENT

As described in ICH Q14, the change management process for analytical procedures involves several key steps to systematically assess and implement modifications.

1. A risk assessment is conducted to evaluate the significance of the proposed change. Factors such as the complexity of the test, the extent of the modification, and the relevance of the analytical procedure to product quality are considered to classify the change as high-, medium-, or low-risk (after risk mitigation, if appropriate). Product and process knowledge should be reviewed along with prior knowledge on the analytical technology to understand potential impact on the performance of the modified analytical procedure. Representative samples should be available to enable bridging studies and build understanding of the revised analytical procedure and the analytical procedure control strategy.
2. Confirmation of analytical performance criteria according to the ATP ensures that the modified method remains fit for the intended use. Appropriate validation studies are conducted to finalize the new analytical procedure description, including parameters for system suitability and the analytical procedure control strategy if needed.
3. Bridging studies are designed to assess the new procedure against the existing one.
4. The impact of the change on regulatory reporting requirements is assessed, determining whether a notification or prior approval regulatory submission is required; reporting requirements might be lower if tools such as established conditions (ECs) or post-approval change management protocols (PACMPs) have been agreed upon in advance with the regulatory authorities.
5. Finally, the change can be implemented after the regulatory actions have been completed for each region, which can take years if multiple regions require prior approval for the change. Varying regulatory expectations for bridging study design and data for submissions can lead to complex and expensive need to segregate inventory or duplicate testing, ultimately increasing costs for patients and the risk of stockouts.

Thus, harmonization of global regulatory requirements is crucial for streamlining the analytical procedure change process and ensuring consistency in regulatory expectations across regions.

Harmonization benefits everyone by ensuring a robust drug supply, preventing shortages, enabling greener approaches in the QC lab, incorporating improved analytical technologies for product control, and improving overall regulatory efficiency by removing the burden of reviewing low-risk changes from regulators so they can focus their efforts on higher-risk changes. By not embracing and implementing Q14 concepts, QC labs may continue to use outdated analytical procedures that lack the ability to keep up with state-of-the-art technologies.

PRACTICAL APPLICATION OF ICH Q12 CONCEPTS

Building on the examples provided in the Annex to Q14, we provide additional examples to illustrate the practical application of concepts introduced in ICH Q12 and described in more detail in ICH Q14, such as ECs and PACMPs, that have the potential to greatly facilitate post-approval changes to analytical procedures. These examples include:

1. A demonstration of how the description of enhanced development can justify established conditions with the potential to make changes in the analytical procedure parameters and end-point detection technology for monitoring dissolution of a solid oral dosage product,
2. A proactive example where it is known at the time of registration that an analytical procedure change will be required, so a PACMP could be utilized for implementing a new analytical procedure for the determination of assay for a solid oral dosage product,
3. An example of navigating a required change in an analytical procedure due to discontinuation of a key component for executing a test for carbohydrate analysis for a biologic product,
4. An example of responding to an instrumentation/technology change for charge variant measurements in biologic products, including sub-examples of differences in result impact, and
5. An example of continual improvement where the robustness of the platform analytical procedure for protein concentration determination is enhanced to ensure reliable execution.

The following examples demonstrate a diversity of analytical procedure changes, encompassing different modalities and scenarios, from simple to complex.

EXAMPLES OF IMPLEMENTATION

EXAMPLE 1

Change in Endpoint Detection Technology for Dissolution Testing of a Solid Oral Dosage Form

This example is a description of an actual interaction between an applicant and a health authority. The applicant provided enhanced understanding of a dissolution procedure to justify their risk-based approach for the proposal of ECs and reporting categories. Through discussion with the health authority, the ECs were accepted, and the outcome is found below.

Dissolution procedures consist of an involved sample preparation (the dissolution step) followed by an "analytical finish," or end analysis step, which incorporates sample handling and an analytical procedure used to determine the amount of drug substance dissolved during the dissolution step [5]. The parameters of a dissolution step (e.g., dissolution apparatus, media, agitation rate) are often critical to the performance of this routine control test for drug products to assure consistent product quality. Dissolution is typically considered a CQA for solid oral dosage products because failure to meet this CQA may impact in vivo performance [6]. When applying the concepts described in ICH Q14, Figure 2, "A risk-based approach for identification of ECs and reporting categories for associated changes in the enhanced approach," the parameters of the dissolution step are likely ECs with a prior approval reporting category because they are selected to ensure robustness, reproducibility, and discriminatory capability.

Commonly, spectrophotometric determination and HPLC are the analytical techniques used to analyze the dissolved drug substance in a dissolution procedure. Changes in the technology or parameters of the end analysis that do not impact the capability

of the procedure to meet its required performance criteria could be made through an enhanced understanding of the product and analytical principles. Therefore, adherence to an ATP could allow for parameters of the end analysis to be ECs with a lower reporting category or managed within a sponsor's Pharmaceutical Quality System (PQS).

Table 1 provides a list of the ECs for the dissolution procedure of an immediate release formulation. These ECs and reporting categories were proposed to a regulatory authority, and the agreed-upon reporting categories were described in a Product Lifecycle Management (PLCM) document. As recommended above, the parameters associated with the dissolution step were found to be ECs with a prior approval reporting category. The parameters were justified through robustness data and demonstration of potential discrimination for variant formulations that included high granule size and over-coated granules. Because performance criteria were not established for changes to the dissolution step parameters, the risk of any change was high, and therefore, a prior approval reporting category was proposed.

Performance characteristics and criteria are in place for the end analysis (Table 1). While not described as an ATP at the time of submission (prior to the approval of ICH Q14), the performance characteristics, along with a statement of intended purpose, would comprise an ATP based on the definition in ICH Q14. The risk associated with changes to analytical procedure parameters in the end analysis was reduced by the defined performance criteria. Therefore, a lower reporting category was proposed for these parameters. The selection of HPLC as the analytical technique and the associated procedure parameters were determined based on prior knowledge of the drug substance properties (including UV profile), impurity and degradation profile (including acceptance criteria of impurities in drug substance and drug product), and properties of the excipients.

Two examples of end analysis parameters that were agreed to as ECs are described below, along with potential changes to the ECs that may occur during the lifecycle of the product and procedure. If these changes were to be made post-approval, the applicant, now the marketing authorization holder, would need to perform a risk assessment to evaluate the potential impact on the performance characteristics and the link to the CQA, complete necessary development, execute bridging studies used to demonstrate adherence to the performance characteristics, which can include validation of the performance characteristics affected by the change.

- **Chromatography Column C18 (USP L1):** A change in this EC to another column outside C18 (USP L1) may be needed due to column availability or performance. The risk for this potential change was assessed to be medium due to knowledge of the product. The levels of drug impurities and potential degradation products would not interfere with accurate quantitation of the active component, so a rapid method can be utilized without the need for a complicated separation. From the risk assessment, the existence of performance characteristics and prior knowledge would facilitate the design of a bridging study and thus enable the reporting category to be reduced to 'notification low' with regulatory agreement.
- **Detection Method Principle—Chromatography:** A quality control laboratory preferred UV spectroscopy over chromatography to allow for a greener technique and fully automated dissolution. In the risk assessment, this potential change was proposed as a medium risk. The risk for this change in technique was not considered high due to: a) an understanding that levels of drug impurities and potential degradation products would not interfere with accurate quantitation of the active component, and b) the detection wavelength was a separate EC and would be maintained or evaluated with a change in technique. As described above for the column change, performance characteristics and prior knowledge that would permit the design of an appropriate bridging study exist, therefore the risk level was reduced, and the reporting category was agreed to as 'notification low'.

EXAMPLE 2

Utilizing PACMP for Implementing a New Analytical Procedure for Determination of Assay for a Solid Oral Dosage Product

Rapid development of drugs for areas of unmet medical need [7] leaves little time to define the analytical control strategy and ensure the robustness of analytical procedures following the finalization of the product control strategy. In these cases, the analytical procedures provided in the commercial filing may need to be updated shortly after approval of the marketing application to ensure robust analytical procedures are in place for the lifetime of the drug.

As defined in ICH Q12, a PACMP is a viable pathway to facilitate anticipated changes via predetermined approaches that may reduce the burden on regulatory authorities and Marketing Authorization Application (MAA) holders. It involes submitting a protocol to the regulatory authority describing the proposed change, rationale, proposed studies, acceptance criteria, and the proposed reporting category. Once approved, the studies are conducted and, if the results meet the acceptance criteria, the information is submitted to the regulatory authority per the protocol's reporting category. Depending on the category, regulatory approval may be required before implemention.

As a demonstration of this approach, the following example is presented. A small molecule, solid oral drug candidate was clinically successful in reducing solid cancer tumors in an area of unmet medical need. This molecule was discovered and developed by a small biotechnology company with limited resources and was then acquired by a major pharmaceutical company less than a year before MAA submission.

The experience with the analytical procedure for assay of the active pharmaceutical ingredient (API) in the drug product was reviewed to assess the robustness of the procedure, and it was determined that the procedure had significant robustness issues. These included peak elution order shifts, peak shape erosion, and

Table 1: ECs of a dissolution procedure for an immediate-release drug product formulation.

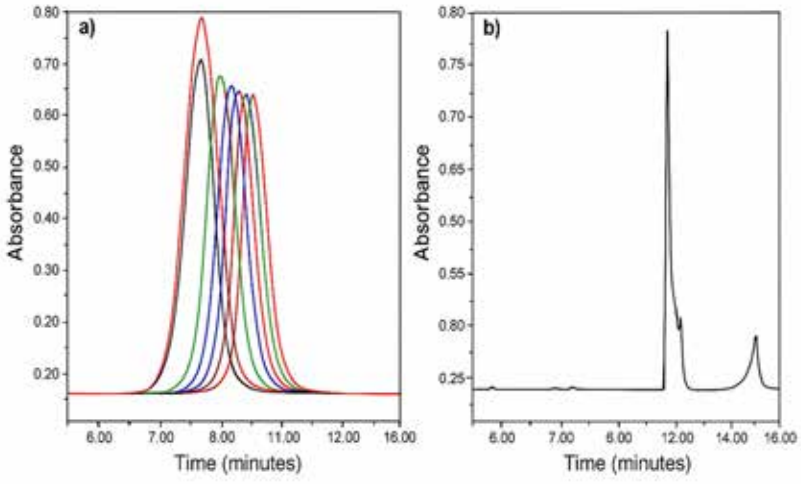
CTD Section	Established Condition		Proposed Change Reporting Category
3.2.P.5.2	**Dissolution Step:**		Prior Approval
	Apparatus: USP Apparatus I (baskets)		
	Dissolution Medium: 50 mM sodium acetate, pH 5.0, de-aerated		
	Volume: 900 mL		
	Temperature: 37.0 ± 0.5 °C		
	Agitation Rate: 50 rpm		
3.2.P.5.2 Dissolution Rate Test	Performance Characteristics for End Analysis: Accuracy: Mean recovery of active ingredient is 97-103% Precision: Overall %RSD of all accuracy values ≤ 2% Specificity: Interference ≤2.0 % after compensated by blank Reportable Range: Minimum 50% of the lowest strength to 125% of the highest strength		Prior Approval
	Detection Method Principle: Chromatography	Change of end analysis principle from chromatography to UV spectroscopy	Notification Low
		Change of end analysis principle from chromatography to any technique other than UV spectroscopy	Prior Approval
	Technology- Specific Analytical Procedure Attributes: Specificity, system precision, linearity, filter suitability, solution stability, range, and robustness Tighten (Non-Reportable)		Notification Low
	Wavelength: 322 nm		Notification Moderate
	System Suitability Test: Injection Precision ≤ 1.5% RSD for active component Peak Asymmetry ≤ 3.0 USP tailing for active component		Notification Low
	Chromatography Column: C18 (USP L1) (i.e., a change to a different reversed phase column outside of USP L1)		Notification Low
	Mobile Phase: (80/20, v/v) Buffer Solution/Acetonitrile Buffer Solution: 0.15% phosphoric acid and 0.1% of ammonium hydroxide in water, pH 2.5 ± 0.2		

short column lifetime (see Figure 1). A detailed risk assessment was conducted that identified analytical procedure risk as an item to be addressed post submission.

To ensure the quality of the measurement in the interim, additional controls were put in place to confirm method performance. These controls consisted of enhanced system suitability requirements to confirm peak elution order (using impurity marker solutions) and peak shape, and an enhanced column wash program to improve overall robustness and column lifetime. Furthermore, a shorter assay method was desired by the commercial QC laboratory to reduce overall analysis time, reduce solvent consumption, and enhance laboratory efficiency, as the assay is employed frequently during batch analysis and stability for determination of multiple CQAs (i.e., identity, assay, uniformity of dosage units, and dissolution endpoint determination).

As noted above, by including a PACMP in the initial MAA, the sponsor can obtain agreement with regulators on what information is required for a change and the reporting requirements, resulting in more efficient implementation of CMC changes while reducing regulatory burden. This hypothetical example outlines the details ideally included in a PACMP, submitted as part of the MAA, and approved by regulators.

Figure 1: Example challenges with the analytical procedure robustness. a) Overlay of chromatograms demonstrating retention time shifting and band broadening that could occur during a typical analysis (7-hour run of 40 injections), b) Example chromatogram demonstrating peak splitting that could occur as a column begins to fail.



An ATP, outlined in Table 2, is defined and included in the PACMP. The approach detailed in Q14 is used to identify ECs for the revised procedure, and a risk assessment is conducted to categorize changes to ECs into high-, medium-, or low-risk levels. Each risk category is then associated with a specific reporting category for changes, whereby the high-risk category necessitates prior approval, and the low-risk category translates to minor notifications, such as inclusion in an annual report, as demonstrated in Table 3.

The PACMP would also include detailed studies proposed to identify the revised analytical procedure conditions. It is assumed in this scenario that the MAA holder employed enhanced approaches to develop the new analytical procedure. The PACMP would include a detailed description of experiments aimed at thoroughly understanding the chromatographic operating-space, including the generation of samples representative of process impurities and degradation products in addition to samples for screening. The steps undertaken to select analytical procedure conditions that are robust against typical sources of variability are also delineated.

The PACMP would also include a commitment to validate the new analytical procedure to meet the expectations outlined in ICH Q2(R2). The final step in fulfilling PACMP requirements would involve the execution of a bridging exercise. This hypothetical scenario involves a comparative analysis of multiple samples that represent the variability of the manufacturing process against predefined acceptance criteria.

The experimental design of this study is listed in Table 4, and the summary of results from the execution of this study is listed in Table 5. Since the acceptance criteria were met, the proposed reporting category for the method change would be designated as 'notification low' and the regulatory submission would be made accordingly.

This example shows how a PACMP and ECs with elements of ICH Q14 may be leveraged to proactively implement anticipated changes to analytical procedures. These approaches are valuable for both the MAA holder and regulatory authorities as they reduce the burden on each organization and the time required for implementation of these value-added changes. Broader application of these ideas will enable analytical procedure robustness and result in enhanced supply chain integrity, which ultimately serves patients.

EXAMPLE 3

Retrospective Case: Managing Carbohydrate Analysis Before ICH Q12/Q14

A retrospective example is presented for a change management scenario for an analytical procedure which was approved before adoption of ICH Q12 and Q14. The procedure was Fluorophore-Assisted Carbohydrate Electrophoresis (FACE) gel analysis of N-linked carbohydrates for a protein therapeutic registered in multiple jurisdictions. The procedure involved enzymatic release of carbohydrates, fluorescent labeling, and resolution and quantitation by gel electrophoresis. The pre-cast FACE gels used for analysis were sourced from a single supplier who announced limited supply and potential discontinuation of the product, necessitating the company to promptly identify backup options.

The ATP for the procedure is listed in Table 6. It takes into consideration the performance needed to ensure sufficient process control and quality of this attribute.

In response to the supply challenge, a chromatography-based fluorescence-labeling oligosaccharide profiling method was developed using anthranilic acid (AA) labeling with HPLC separation. This technology represented an industry standard with improved sensitivity and precision, as well as enabling faster development through in-line oligosaccharide identification by mass spectrometry [6]. The development included comprehensive identification and mapping of all oligosaccharide species between the FACE and chromatography-based methods (see Figure 2).

Table 2: ATP for assay of solid oral dosage form.

Intended Purpose	
Quantification of the API in drug product for release and stability	
Link to CQA (Assay)	
Analytical procedure should quantitate API in drug product to verify the CQA of assay values between 90.0-110.0%	
Characteristics of the Reportable Results (performance characteristics)	
Characteristic	Acceptance Criteria
Accuracy	Recovery between 98.0% to 102.0% at three levels 80%, 100%, and 120% of nominal concentration; %RSD ≤ 2.0% at each level
Precision	%RSD for intermediate precision samples ≤ 2.0% for each analyst %RSD for intermediate precision samples ≤ 3.0% for both analysts combined
Specificity	Method is capable of separating impurities (process impurities and degradation products) from API. Any interference from placebo components is < 0.5% of the nominal concentration of the API.
Reportable Range	High level: 70 — 130% of nominal

Table 3: Evaluated risk, proposed established conditions, and proposed reporting categories.

Established Condition	Overall Risk Category	Reporting Category	Justification/Rationale
ATP	High	Prior Approval (PA)	If widening the ATP is necessary, it will be reported as PA.
Technology: HPLC	Low	Notification Low	ATP must be met, defined bridging strategy must be met using representative materials.
System suitability tests (SST) SST 1: system precision SST 2: blank interference SST 3: resolution SST 4: peak symmetry	Low	Notification Low	SST were established based on a risk assessment and considering compendial expectations. A change to SST should ensure similar control of the factors listed.

Table 4: Experimental design that could be leveraged in a bridging study between existing and proposed analytical procedures.

Setup	Day	Analyst	HPLC	Batch Number
1	1	A	1	1, 2
2		B	2	3, 4
3	2	A	2	3, 4
4		B	1	1, 2
5	3	A	1	3, 4
6		B	2	1, 2

Table 5: Summary results from execution of bridging study between existing and proposed analytical procedures.

Method	Mean % Label Claim
Current method	99.9
Proposed method	100.3
Absolute Difference	0.4
Acceptance Criteria	NMT 1.4
Result	Pass

The new procedure was demonstrated to meet the ATP requirements through validation studies. Extensive bridging studies were conducted between the FACE gel- and chromatography-based methods. Statistical correlation was demonstrated across large-scale batches, as well as with carbohydrate-remodeled samples engineered at small-scale, which provided a robust dataset for comparison. These bridging studies established the correlation between the two methods.

Under the regulatory framework at the time, the sponsor submitted prior-approval applications to multiple regulatory authorities to implement the method change and adjust acceptance criteria. This process required significant resources and time before implementation could occur across all markets.

In retrospect, this example provides an opportunity to consider how ICH Q12 and Q14 principles could have facilitated a more efficient change management process.

The following considerations might have been made, taking into consideration the risk assessment described in ICH Q14's Figure 2:

1. The method performance characteristics and acceptance criteria would be considered ECs.

Table 6: ATP for analysis of N-linked carbohydrates.

Intended Purpose	
Relative quantitation of main N-linked carbohydrate species in product Drug Substance A.	
Link to CQA	
The main carbohydrate species is important for receptor binding and potency of the therapeutic.	
Characteristics of the Reportable Results (performance characteristics)	
Characteristic	Acceptance Criteria
Precision	RSD of the main N-linked carbohydrate species percentage < 5% as measured by intermediate precision studies.
Specificity	Method is capable of resolving main carbohydrate species from the remaining species. Specificity demonstrated by identification of carbohydrate species using orthogonal procedure (off-line or in-line mass spectrometry)
Linearity and Range	Linearity of response demonstrated across the specification range for the main carbohydrate species, $R^2 \geq 0.98$.
Accuracy	Leveraged by demonstration of precision, specificity, and linearity. Practical consideration for demonstrating any statistical offsets through appropriately powered bridging studies.

2. The risk associated with the change to the procedure would initially be considered high based upon impact of oligosaccharide structure on clinical efficacy.
   a) Enhanced product knowledge of the relationship between carbohydrate structure (the CQA measured by the method) and potency was presented in the dossier, with the correlation confirmed using carbohydrate-remodeled samples for both methods. This knowledge included an understanding of the relationship between potency and carbohydrate structure, and the detectability of potency changes by the *in vitro* potency method on release.
   b) Enhanced understanding of the method was presented in line with ICH Q14 principles. Identities of carbohydrate structures were mapped between the methods. Robust method control was demonstrated with an enhanced understanding of separation mechanism, including column-to-column ruggedness, which improved the risk profile of single-vendor sourcing, as encountered with FACE gels. Based on the product and method understanding, the risk associated with the changes would be considered medium.
3. The extensive, successful bridging studies (n = 44 batches), successful method validation, and strong statistical correlation between the methods lowered the overall risk level for the change. This demonstrated sufficient understanding of the procedure bias and precision to confirm adherence to specifications. Taken together, these considerations may have supported a case for 'notification moderate' (with prior agreement from the regulatory agencies), rather than the prior approval path that was followed.
4. The superior performance of the new method compared to the filed FACE method, and adherence to the ATP further supported the change.

This retrospective example reinforces the utility of how ICH Q12 and Q14 principles provide a framework for a risk-based approach to change management. The extensive method bridging, thorough understanding of the analytical targets and product, and superior performance of the new method all are successful risk reduction approaches and highlight how this change should have been readily implementable under a more streamlined regulatory pathway.

Under the current environment with Q12, a PACMP containing the ATP could be proactively submitted to multiple jurisdictions which could drive agreed-upon lowered reporting categories and simultaneous implementation. This retrospective analysis highlights the value of the ICH Q12 and Q14 guidelines in facilitating science- and risk-based approaches to pharmaceutical change management, ultimately supporting continual improvement and innovation in analytical methods while maintaining product quality.

EXAMPLE 4

Instrumentation/Technology Change – Charge Variant Measurements in Two Biologics

The enhanced approach described in ICH Q14 provides a workflow to allow flexibility in instrument choice with reduced regulatory impact, including for commercial products. Here, we use the measurement of charge variants in biologics drug products as an example of where this flexibility may be beneficial.

The charge profiles of biologic products are indicative of product manufacturing consistency and product stability over time under different conditions. They may also be used to directly or indirectly to monitor specific product CQAs upon release and stability testing. Imaged capillary isoelectric focusing (icIEF) is an electrophoretic technique that uses differences in isoelectric point (pI) to separate and monitor charge variants. In addition to ion exchange chromatography (IEX), icIEF is widely used across industredilry as a release and stability assay for biologic drug substances and drug products.

Recently, the vendor of the commercially available and widely used icIEF iCE3 instrumentation announced discontinuation of support for the iCE3 due to the release of the updated icIEF Maurice model. The differences between the systems are primarily related to the ease of use and not the mechanism of separation/detection, though the newer model does also allow an alternative

detection mode (native fluorescence) with higher sensitivity than the traditional UV detection [8].

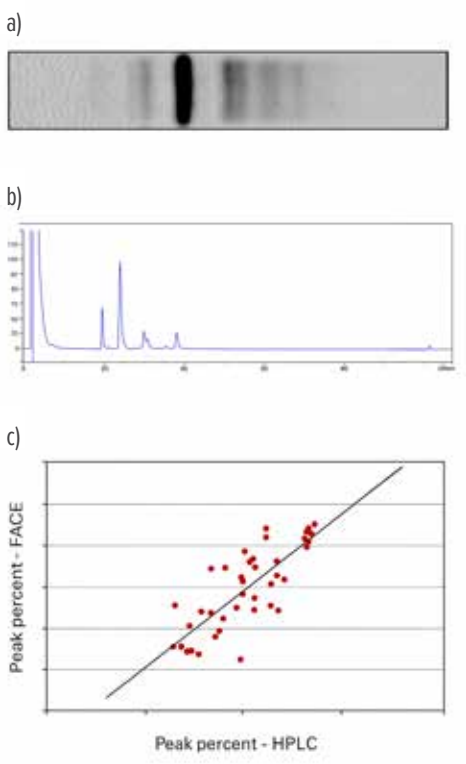
While the vendor of these two instruments has authored technical notes establishing comparability [8], at least one recent paper [9] has highlighted differences between iCE3 and Maurice instrumentation for a biologics drug product, indicating that bridging still needs to be demonstrated on a case-by-case basis and could result in additional changes to the analytical procedure conditions (such as, master mix (ampholytes, standards, etc.) composition, digestions or conditions for sialylated or other non-traditional molecules, or minor changes in instrument parameters). For several molecules the instruments are equivalent, with no changes to conditions, and the two instruments can be used interchangeably [8, 10]. However, in some cases, the instruments result in different profiles that require evaluation of product release and/or stability specifications (see Figure 3). Changes to specifications are by default high risk requiring prior approval per ICH Q12.

Table 7 indicates the instrument parameters used for the side-by-side iCE3 and Maurice analysis of two biologics, Product A and Product B. Parameters were kept as similar as possible for the comparison, with one minor change in autosampler temperature for Product A due to stability observations over long runs, and cartridge and sample injection load changes for both products as required to accommodate the model change.

The left side of Figure 3 illustrates a biologics program, Product A, with no significant impact to profile or results from the change in instrument model from iCE3 to Maurice. Figure 3c shows overlays of Product A with no stress (0x) and 2x light stress on both iCE3 and Maurice. While minor changes, such as improved peak resolution in Maurice, are observed, the profiles are overall comparable. Furthermore, the box plot in Figure 3a shows that the reportable results are not impacted by the change, as the % area differences between the two models hovers around zero for the Acidic, Main, and Basic species. For programs similar to Product A, where there is no significant impact on the profile or reportable results, or differences fall within the variability of the method, comparability between the iCE3 and Maurice should be documented through either development and/or bridging studies. No formal change needs to be reported to the agency; the change should instead be documented and managed through the internal PQS.

The right side of Figure 3 shows another biologics program, Product B, that did have observed differences in the profiles between the iCE3 and Maurice instruments, leading to changes in reported results (see Figure 3d). The transition to the Maurice causes shifts in % area of Main and Basic species, evident in both the control sample (0x stress) and more apparent in the 2x light stress samples. While the overall species observed are similar between the two models, relative amounts of the different species differ as indicated by the % area differences shown in the box plot in Figure 3b. Specifically, the average % Basic species was observed to have an ~5% increase, on average, for Maurice as compared to iCE3 with a concurrent ~5% decrease in Main. Acidic species were similar between the two models. Shifts in profile similar to that observed for Biologics

Figure 2: Profile comparison of (a) FACE gel analysis, (b) AA-Labeling/HPLC analysis, (c) combined correlation analysis of HPLC vs. FACE results across small- and large-scale lots (n = 44).



Product B can result in changes to the specification, in which case prior approval would be required prior to implementing the change consistent with ICH Q14 recommendations. Additional details on the potential risk and reporting categories are summarized in Table 8.

EXAMPLE 5

Continual Improvement of a Platform Analytical Procedure for Protein Concentration Determination

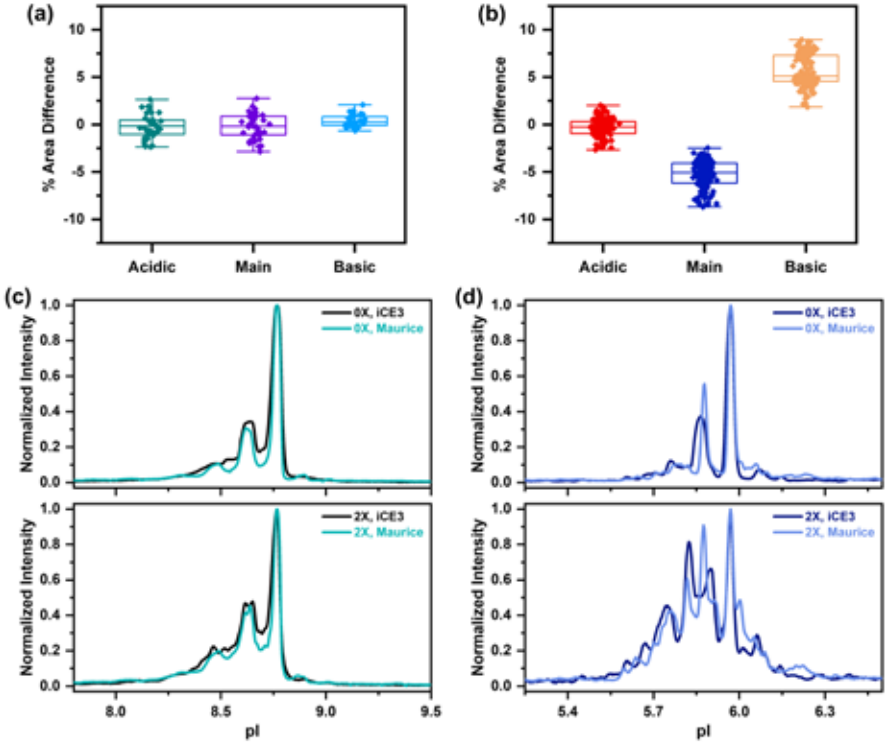
The CTech™ SoloVPE® has become a standard industry approach for measurement of protein concentration [11]. Through a variable pathlength approach, the SoloVPE® instrument enables UV/Vis measurements of varying solution concentrations without need for manual sample dilutions prior to analysis [12]. SoloVPE® is deployed in QC laboratories as well as in manufacturing plants directly due to ease of execution and minimal manual steps, allowing for real-time in-process testing and at-line measurement. Furthermore, the elimination of manual sample dilution steps presents an improvement in protein concentration result accuracy and precision relative to traditional fixed-path length UV/Vis analysis.

In this case study, a sponsor maintains a single multisite platform analytical procedure for UV/Vis measurement of protein concentration that is used across > 25 commercial and > 30 clinical products, across stages of manufacture and QC testing, at five global manufacturing and testing facilities. Now supported by ICH Q14 and

Table 7: Instrument parameter comparison between iCE3 and Maurice for biologic Products A and B.

Parameter	Product A		Product B	
icIEF System	iCE3	Maurice	iCE3	Maurice
Cartridge	Fluorocarbon Coated icIEF Cartridge	Maurice icIEF Cartridge	Fluorocarbon Coated icIEF Cartridge	Maurice icIEF Cartridge
Focus Period	Focus Period 1: 1 min at 1500 V Focus Period 2: 7 min at 3000 V	Focus Period 1: 1 min at 1500 V Focus Period 2: 8 min at 3000 V	Focus Period 1: 1 min at 1500 V Focus Period 2: 9 min at 3000 V	Focus Period 1: 1 min at 1500 V Focus Period 2: 9 min at 3000 V
Autosampler Temperature	10 °C	4 °C	10 °C	10 °C
Sample Injection Load	Transfer Time Plateau + 40 s / 2000 mBar	90 s	Transfer Time Plateau + 40 s / 2000 mBar	55 s

Figure 3: icIEF of biologic Product A and B measured using iCE3 and Maurice. The box plots of % area of Product (a) A and (b) B obtained by subtracting the % area of samples obtained using iCE3 from those using Maurice. The electropherograms of biologic Product (c) A and (d) B subjected to up to 2× light exposure where 1× corresponds to 200 watt hours/m2 of UV energy and 1.2 million lux hours of white light according to ICH Q1B guideline.



ICH Q2(R2), leveraging a platform analytical procedure allows for enhanced global consistency and a streamlined process for method qualification and transfer. However, the method's widespread use prompts complex regulatory reportability assessments whenever an improvement to the method is considered.

The SST for the platform procedure employs a proprietary chemical standard (CHEM013) from CTech in two tests: a 280 nm test and a 310 nm test. The purpose of the 280 nm test is to assess the capability of the SoloVPE® usolonit to take accurate and precise measurements using its automatic path length optimization algorithm at the wavelength at which proteins are measured. The purpose of the 310 nm test is to assess the operation of the SoloVPE® unit at the minimum path lengths within its range, thus representing analysis of a highly concentrated sample. This approach has successfully allowed for routine verification that the instruments are suitable for their intended analysis. However, it has also contributed to a high assay invalid rate, impacting the operational efficiency of test laboratories and manufacturing plants.

Assay invalids occurred when the 310 nm Fixed-M test failed to produce responses with sufficient linearity, due to low absorbance

Table 8: Evaluated risk, proposed established conditions, and proposed reporting categories.

Established Condition	Overall Risk Category	Reporting Category	Justification/Rationale
Technology: Model update from iCE3 to Maurice with no significant impact to profile/ reported results.	Low	Not reported; managed through PQS.	No significant impact to profile/pI/reported results thoroughly demonstrated through bridging using representative materials. ATP is therefore still fully met, and instruments can be used interchangeably assuming comparability established.
Technology: Model update from iCE3 to Maurice with impact to profile/reported results.	Dependent on the extent of change.	Notification. Prior approval could be required if changes are significant (e.g., require specification update).	Impact of model change demonstrated through bridging using representative materials. Shifts in the profile with impact to %Acidics/Main/Basics reporting should be characterized, including potential impact to specifications and stability. Charge variants are typically identified and characterized during isolation and characterization of impurities workflows prior to commercial filing. This information can be leveraged to determine overall risk of change and understand the impact of method performance on control of product CQAs.

of the CHEM013 standard at 310 nm. To address this challenge an alternative SST was developed using a more concentrated standard (Patent Blue Standard Solution) and leveraging an alternative path length algorithm. This change has been demonstrated to improve the invalid rate and has additional benefits in requiring 50% less time for execution compared to the current SST, and lowering costs due to the need for less standard volume for each SST execution and a lower cost of the standard itself.

For these reasons a change to the analytical procedure was desired, and a regulatory reportability assessment was performed for all products that leverage the method in all regions where those products have been filed (see Table 9).

Considering that four products require approval prior to implementation, an agile strategy was developed to enable immediate implementation of the change for other products while maintaining continued use of a single multiproduct multisite platform method. Within the method, sub-procedures were defined with reference to an external form listing all products and their corresponding sub-procedure. The first sub-procedure leverages the legacy SST, and this procedure will continue to be used to test the four impacted products until the change is approved in regions that leverage AND. The second sub-procedure employs the new SST, which all other products will be able to leverage and benefit from as soon as the quality change control process is completed. Once the change has been approved for all products in all regions, the method procedure will be updated a second time to remove the legacy SST sub-procedure, and all products will then be tested following a single harmonized procedure from that point forward.

While this implementation strategy does grant some relief from the high assay invalid rate, it was recognized that yet another creative strategy will soon be needed for the evolution of the protein concentration method in response to recent news from CTech™ that they will retire the SoloVPE® instrument, ceasing support for it in 2031, and will transition to a new instrument model called the SoloVPE® PLUS system which has lower minimum path lengths, that potentially may trigger yet another SST update, or other analytical procedure modification.

Applying ICH Q12 and Q14 principles could have enabled a faster path to full global implementation of the change, which could have been considered low risk since it does not affect sample analysis or reported results. By sharing the risk assessment with regulatory authorities and securing prior agreement on a low reporting category for these established conditions, duplicate testing could have been avoided. The change could have been implemented through internal change control procedures with appropriate experimentation and documentation, followed by reporting. Alternatively, use of a PACMP covering the SST change for all products could have been an option. Had such a protocol been in place and approved by the various agencies, the new SST could have been immediately implemented for all products. This change did not affect the ATP for the method and was an operational improvement yet still prompted a requirement for approval prior to implementation in certain regions, underscoring the criticality of efforts to drive health authority alignment and innovation during commercial life cycles [4].

CONCLUSION

From the examples presented above, it is evident that managing changes to analytical procedures is a complex and lengthy process. ICH Q14 offers a science- and risk-based framework that streamlines change management while ensuring product quality and regulatory compliance while fostering innovation. Therefore, it is essential to encourage sponsors to utilize and submit the regulatory tools described in ICH Q14 whenever implementation in individual markets has been realized. Furthermore, regulators are encouraged to harmonize change requirements with ICH Q12 so that the industry may fully harness the potential of the ICH Q14 framework. Ultimately, the success of this guidance depends on both adoption into industry practices and supportive regulatory oversight.

The examples demonstrate how an ATP (and other elements of the enhanced approach), ECs, and PACMPs can be leveraged to

Table 9: Summary of regulatory activities required and timing to implement the system suitability test change for the SoloVPE® measurement of protein concentration.

Reporting Category	General Assessment	Expected Implementation
Not reportable to any regulatory agencies.	Method update does not need to be reported in clinical trial applications affected by this change, as this level of detail is typically not registered.	Immediately following change control completion including internal implementation activities.
Reportable with no product restriction.	Annual notification required for approved commercial products in the US and EU.	Immediately following change control completion including internal implementation activities.
Reportable with product restriction. Requires prior approval from a regulatory agency before product distribution.	Full SoloVPE method is described in RU, BY and KZ Analytical Normative Document (AND[1]) and therefore the change to the method requires prior approval in these countries.	Approximately 4-5 years from initiation of the change.

The Analytical Normative Document (AND) is a product-specific registration document required by several markets, including Russia, Kazakhstan, Belarus, and Ukraine, for national licenses and for products registered with the Eurasian Economic Union (EAEU). The AND typically contains detailed information on specifications and analytical procedures. For most products in many regions, the change either does not need to be reported or can be reported post-implementation. However, for four commercial products registered in regions that utilize the AND, the change has been assessed as requiring prior approval. Unfortunately, other mandatory and planned activities (ongoing CMC variations) have affected the timing of filing this method change, resulting in an expected implementation timeline of no sooner than four to five years.

streamline the implementation of necessary changes to analytical procedures, ranging from minor modifications to complete technology updates. These tools allow for appropriate risk categorization and corresponding reporting requirements, reducing regulatory burden for low-risk changes while maintaining appropriate oversight for higher-risk modifications. Harmonization of global regulatory expectations for analytical procedure changes, as facilitated by ICH Q14/Q2(R2) and Q12 tools, is crucial for ensuring a robust drug supply and compliance by minimizing unnecessary duplicate testing using obsolete procedures while awaiting individual regulatory approvals.

By enabling QC laboratories to incorporate state-of-the-art technologies and greener approaches, these guidelines support continual improvement of analytical procedures. As demonstrated across diverse applications—from dissolution testing to complex carbohydrate analysis and charge variant measurements in biologics—this modernized approach to analytical procedure lifecycle management ultimately benefits patients through enhanced product understanding, improved quality control, and more efficient regulatory processes.

The authors recognize the need to further clarify ICH Q14 concepts and principles by providing additional examples. This article marks the beginning of this effort, and we invite readers to contribute more real-life examples to enhance understanding, application, and adoption of ICH Q14.

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For more information about ISPE's PQLI Initiative, visit ispe.org/initiatives/pqli

References

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "ICH Harmonised Guideline: Analytical Procedure Development Q14." 1 November 2023. https://database.ich.org/sites/default/files/ICH_Q14_Guideline_2023_1116.pdf
2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "ICH Harmonised Guideline: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management Q12." 20 November 2019. https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf
3. Zavialov, E., A. Thomas, S. Ramdas, T. Ocheltree, and C. Langer. "ICH Q12: A Transformational Product Life-Cycle Management Guideline." Pharmaceutical Engineering, May–June 2020. https://ispe.org/pharmaceutical-engineering/may-june-2020/ich-q12-transformational-product-life-cycle-management
4. Gellermann G, Kirsch S, den Engelsman J. "Fine-tuning analytical development strategies for every phase." BioProcess Online. 22 March 2024. https://www.bioprocessonline.com/doc/fine-tuning-analytical-development-strategies-for-every-phase-0001
5. United States Pharmacopeia. "General Chapter, "1092" The Dissolution Procedure: Development and Validation." USP-NF. Rockville, MD, US. (2021).DOI: https://doi.org/10.31003/USPNF_M643_05_01
6. European Medicines Agency. "Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action." 10 August 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-dissolution-specification-generic-solid-oral-immediate-release-products-systemic-action-first-version_en.pdf
7. US Food and Drug Administration. "Fast track, breakthrough therapy, accelerated approval, priority review." 12 June 2023. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review
8. Bio-Techne. "iCE4 and Maurice Data Comparability Evaluated Using Three Biomolecules." https://www.bio-techne.com/resources/literature/ice3-and-maurice-data-comparability-for-three-biomolecules
9. Wen X, Liu AP, Song J, et al. "Enzymatic Desialylation Enables Reliable Charge Variant Characterization of Highly Glycosylated and Sialylated Fc Fusion Proteins." ACS Pharmacology and Translational Science. 23 January 2025;8(2):394-408. doi: 10.1021/acsptsci.4c00460
10. Salas-Solano O, Kennel B, Suhr PS, et al. "Robustness of iCIEF Methodology for the Analysis of Monoclonal Antibodies: An Interlaboratory Study." Journal of Separation Science. November 2012;35(22):3124-9. doi: 10.1002/jssc.201200633. Epub 2012 Oct 15.
11. Shih E, Salerno M. "The Power of Slope Spectroscopy." C Technologies Inc., Bridgewater, New Jersey, US; 2 September 2020. https://ctech.repligen.com/wp-content/uploads/2021/03/The-Power-of-Slope-Spectroscopy-1.pdf
12. Ferraiolo MT, Ferraiolo J. "Evaluation of the Slope Spectroscopy Method for Protein Concentration Measurment of Monoclonal Antibodies." American Pharmaceutical Review. September/October 2021, pp. 1-6. https://www.repligen.com/Products/analytics/solovpe-protein-a280/Evaluation-of-the-Slope-Spectroscopy-method-for-Monoclonal-Antibodies.pdf

13. Dhume ST, Anumula KR. "High Resolution and High Sensitivity Methods for Oligosaccharide Mapping and Characterization by Normal Phase High Performance Liquid Chromatography Following Derivatization with Highly Fluorescent Anthranilic Acid." Glycobiology. 1998;8(7):685–694. https://pubmed.ncbi.nlm.nih.gov/9621109/

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READINESS FOR IMPLEMENTATION OF ICH Q2(R2) AND Q14

Industry Survey Results

By Qinggang Wang, PhD, Bryan Castle, PhD, Timothy W. Graul, PhD, Nina S. Cauchon, PhD, Gerald Gellermann, PhD, and Mary Beth Pelletier, PhD

The International Council for Harmonisation (ICH) Q2(R2) and Q14 guidelines, finalized in late 2023, outline strategies for analytical procedure development, validation, and lifecycle management. As global implementation progresses, ISPE's PQLI® Analytical Method Strategy Team surveyed industry stakeholders in mid-2024 to assess readiness, identify opportunities, and highlight areas needing alignment between sponsors and regulators. Survey results indicate the new guidelines offer significant opportunities, though some challenges remain. Continued collaboration between sponsors and regulators is key to ensuring the guidelines have the greatest impact for improved and streamlined implementation and maintenance of analytical procedures.

The ICH guidelines Q2(R2) (a revision of Q2(R1), "Validation of Analytical Procedures" [1] and Q14 "Analytical Procedure Development" [2] reached step 4 of the ICH process on 1 November 2023. ICH regulatory members are expected to implement all harmonized ICH guidelines within their respective countries or regions. To date, the guidelines have been implemented by the European Commission (EC), US Food and Drug Administration (FDA), the Swiss Agency for Therapeutic Products (Swissmedic), the Egyptian Drug Authority, and the National Medical Products Administration (NMPA) in China. Argentina and Turkey have implemented Q14 and Saudi Arabia has implemented Q2. Historically, some non-ICH regions have adopted the guidelines as well.

To assess industry readiness for implementation and to understand challenges, opportunities, and overall preparedness of industry professionals, the ISPE-PQLI Analytical Method Strategy (ICH Q2(R2)/Q14) team conducted a comprehensive survey. The survey was conducted anonymously from 18 April to 15 July 2024, and received 201 responses. Of these, 57 provided answers to questions beyond demographic information and are discussed below. These responses, along with other optional free-text comments, are summarized, and the key findings and takeaways are presented.

SURVEY METHOD

The survey was developed by the ISPE-PQLI Analytical Method Strategy (ICH Q2(R2)/Q14) team to gauge awareness and implementation of the revision to ICH Q2 and the new guideline, ICH Q14. The survey contained 29 multiple-choice questions, with some requesting additional short comments. ISPE sent the survey by email to over 8,000 individuals in the ISPE database that met the criteria based on business category, job title, and job function. The email was sent on 18 April 2024 with the survey remaining open until 15 July 2024. During that period, the survey link was promoted on ISPE social media platforms, in an e-newsletter, and a blog post. Because the intent of the survey was to gather data from individual contributors rather than companies' consensus, responses were collected anonymously, and the companies of the responding individuals are unknown.

Survey Response Demographics

In response to the question "What role(s) does your company/organization have within the pharmaceutical industry?", survey respondents self-reported to represent companies in multiple sectors within the pharmaceutical industry (see Figure 1). Responding organizations spanned users of the Q2(R2) and Q14 guidelines, including pharmaceutical manufacturers (innovator, biosimilar, generics, and contract manufacturing organizations), raw material and excipient suppliers, contract analytical testing labs, and analytical equipment manufacturers, as well as CMC consulting and global pharmacopoeias.

In response to the question, "What is your role(s) related to

Figure 1: The diversity and representativeness of the survey sample by organization type.

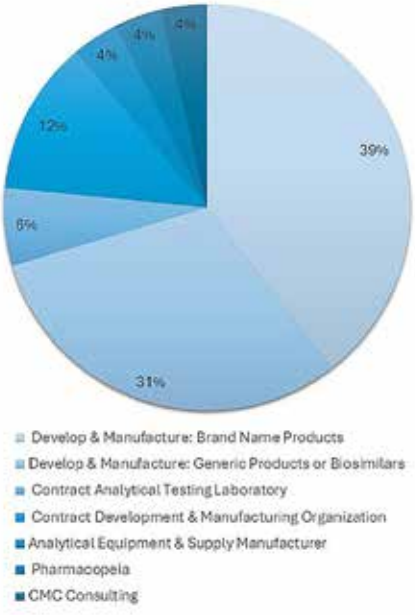
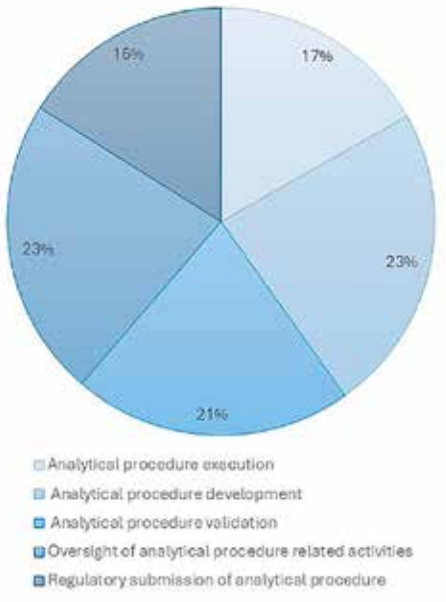


Figure 2: The distribution of job functions or responsibilities of survey respondents was spread across different areas within their organizations. Beyond the predefined categories, respondents also identified other relevant roles, showing the diverse expertise involved in analytical procedure work. These roles included: statistical support, IT, data analytics, and quality assurance.

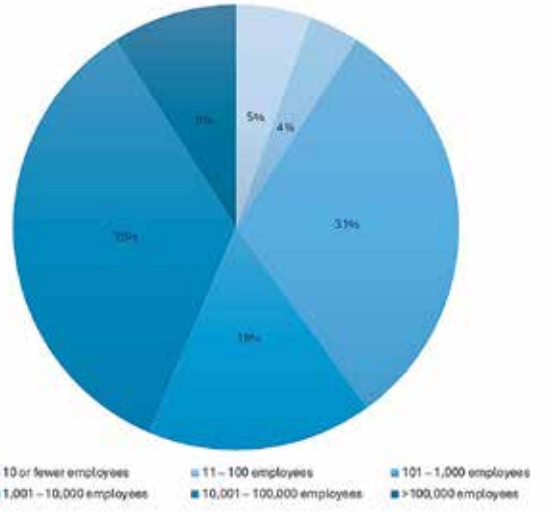


analytical procedures?", respondents reported that they held diverse roles within their companies, including analytical development, analytical procedure validation and/or lifecycle management, quality assurance, statistical analysis, regulatory, and IT (see Figure 2). A significant portion of participants were involved in method development, validation, and/or execution, reflecting the survey's focus on guidance related to the lifecycle of analytical procedures. Quality assurance and regulatory affairs professionals also constituted a substantial segment of respondents, reflecting that these guidelines impact technical, compliance, and regulatory elements of analytical procedure management.

Respondents represented organizations of varying sizes from fewer than 10 to over 100,000 employees (see Figure 3). The data indicate a balanced representation across small, medium, and large organizations, reflecting the ubiquitous nature of the guidance and that the survey findings are applicable to a wide range of company sizes within the industry.

The respondents reported that their companies manufacture and/or test products including small molecules, biologics, cell/gene therapies, vaccines, combination products, analytical equipment, excipients, and raw materials, siRNA therapeutics, active pharmaceutical ingredients, isotopes, and generic formulations (respondents could select more than one category). Figure 4 highlights the diversity of product types managed by respondent organizations. Small molecules were the single highest category reported (29%), however, there is notable representation of biologics, cell/gene therapies, and vaccines, as well as combination products, reflecting the industry's expanding focus on biologically derived therapeutics and complex modalities.

Figure 3: Company size distribution.

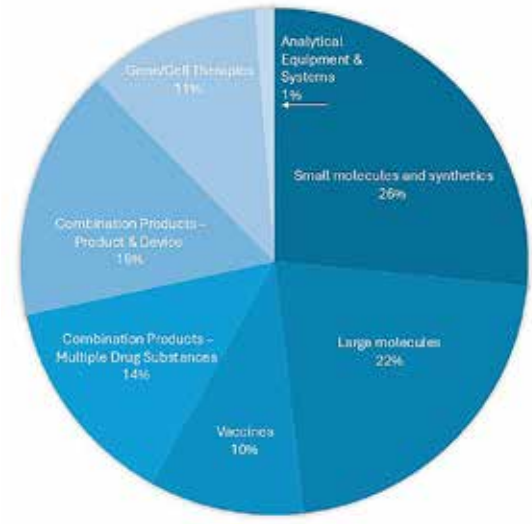


KEY SURVEY QUESTIONS AND FINDINGS

Opportunities, Challenges, and Perceived Risks in Implementing ICH Q2(R2)

Respondents were asked to provide feedback on the challenges and/or risks associated with implementing the revised Q2 guideline, particularly in light of the newly introduced elements. ICH Q2 has been a foundation of analytical method validation practice since its

Figure 4: Product types manufactured and/or tested by represented organizations.



initial publication in 1994. The revision of this guidance is widely recognized as having the potential to significantly impact ongoing operations. Responses varied from "none" (no risks or challenges) to addressing the many elements of Q2. Topics and scope included:

- **Confidence intervals**
  Setting acceptance criteria, evaluation, and reporting meaningful confidence intervals for accuracy and precision. The industry lacks sufficient guidance on how regulators expect criteria to be defined or data to be assessed—especially for variable methods with limited data availability. Appropriate use of statistical methods remains a concern.
- **Combined accuracy and precision**
  Uncertainty around how to establish meaningful acceptance criteria that integrate both accuracy and precision.
- **Regulatory acceptance of development and platform analytical procedure data**
  Risk that regulatory authorities may not accept data leveraged from prior validations or platform analytical procedures. There is a lack of clarity on the extent of data that can be leveraged from development studies.
- **Robustness**
  Evolving expectations for data quality and submission, particularly given the transfer of robustness-related topics to ICH Q14.
- **Multivariate analytical procedures**
  Challenges in developing initial models and meeting expectations for multivariate calibration.
- **Implementation**
  Questions around how to implement the flexibility afforded by ICH Q14. What level of operational control is required to utilize development data to support robustness? Lifecycle changes to analytical procedures may necessitate partial or full revalidation. Both companies and global regulators may be slow to adopt and implement these changes.
- **Application to legacy products**
  Unclear expectations for the application of revised concepts to legacy (approved) products, and the timing for global compliance with new product requirements.

Respondents shared positive feedback on the clarity and opportunities introduced by Q2(R2), with topics and scope including:

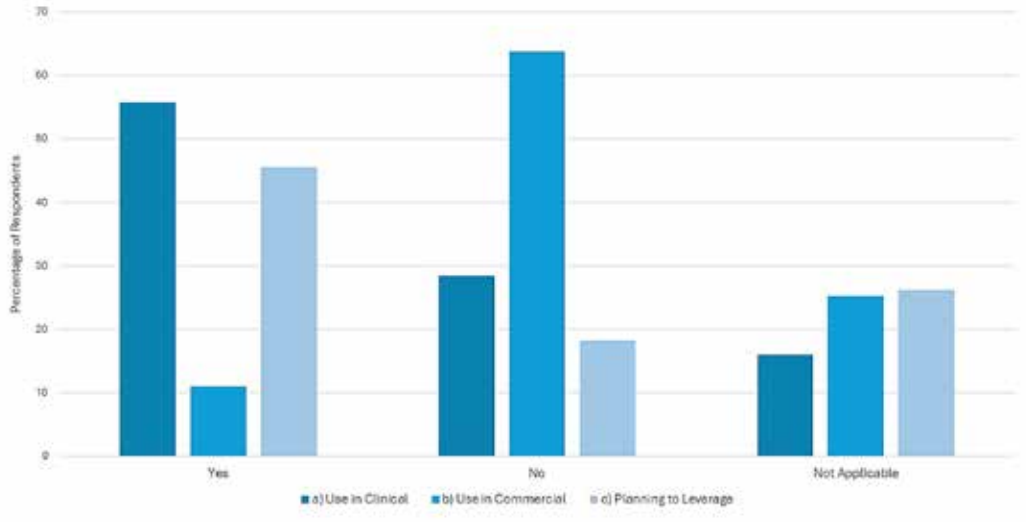
- **Wider variety of analytical procedures and modalities**
  Setting The guideline is directly applicable to a broader range of techniques and modalities.
- **Platform analytical procedures**
  Q2(R2) documents the concept of platform analytical procedures in guidance for the first time, which can enable increased efficiency and harmonization.
- **Prior knowledge and development data**
  Opportunity to leverage where appropriate and not repeat non-value-added studies, and also the opportunity to optimize time investment.
- **Utilization of science- and risk-based justifications**
  Opportunity to justify development and validation approaches versus prescriptive requirements.
- **Utilization of robustness data from development**
  Robustness testing in advance of validation should increase the speed and success rate of method validation.
- **Enhanced approaches to development and link to validation**
  Q2(R2) and Q14 enable increased acceptance of Quality by Design (QbD) approaches for analytical procedures.
- **Multivariate analytical procedures:**
  Clarity of application for techniques such as ICP-MS, FT-NIR, NMR, and direct application to biologics.
- **Combined accuracy and precision**
  General acceptance of the approach.
- **Lifecycle approach for analytical procedures**
  In combination with ICH Q14, validation is a component of lifecycle management. The link between development (Q14) and validation (Q2(R2)) is clear.
- **Clarity of application:**
  Examples in Annex 2 [1] illustrate direct application of ICH Q2(R2) concepts.

Additional insights on these challenges and opportunities are provided through responses to the questions discussed in this article.

Confidence Intervals in Validation

For accuracy and precision assessments in analytical procedure validation, ICH Q2(R1) states that confidence intervals around reported recovery/mean "should be reported" [3]. ICH Q2(R2) expands on this by stating that, "an appropriate 100(1-α)% confidence interval (or justified alternative statistical interval)…should be reported," and that "the observed interval should be compatible with the corresponding [accuracy/precision] acceptance criteria, unless otherwise justified" [1].

Figure 5: Adoption of platform analytical procedures in a) clinical development; b) commercial registrations; and c) plans to leverage common validation results for platform analytical procedures.



Respondents were asked if there were concerns with the updated recommendations for confidence intervals (CI) and the expectation that these intervals be compatible with acceptance criteria. The survey showed that 76% of respondents expressed the following concerns:

- 40% indicated that, due to a limited number of replicate samples in accuracy and precision validation, the confidence intervals may not be meaningful. They noted that this requirement may lead to an increase in the number of replicates needed for accuracy and precision validation.
- 21% stated that there is insufficient experience and data to set appropriate acceptance criteria.
- 16% stated that their organization lacks internal expertise to implement confidence intervals.
- 15% of respondents indicated no concern, noting that they had already implemented CI reporting.

One respondent elaborated in a free-text comment: "We are concerned about the increased risk of failures during validation against a criterion that we don't understand well enough to set meaningfully at this point. We are also concerned that, while we may be able to have scientific discussions about the results with some larger agencies who have more experience with this requirement, we may struggle with smaller global agencies who are also still learning—which could lead to reduced global harmonization vs the ICH goal of increased harmonization."

Considering that there are multiple reasons for industry to be concerned with the implementation of CI reporting as described in Q2(R2), increased dialogue will be necessary between industry and regulators. This could come about through the publication of the ICH training materials [4], webinars, and conference sessions.

Combined Approaches to Accuracy and Precision

ICH Q2(R2) allows for combined approaches for accuracy and precision [1]. The combined approach is also emphasized in the training material (Module 2) published by ICH on the Q2(R2)/Q14 guidelines [4]. Respondents were asked if their companies had already or were planning to leverage combined approaches to accuracy and precision.

The majority (58%) of the participants responded that they are already using or planning to use combined approaches, whereas 40% replied that they are using the conventional approach. "Target Measurement Uncertainty" was mentioned as an approach for the calculation of acceptance criteria. It was commented by one company that both approaches (combined or independent) are available as optional analytical tools. Two responses indicated that the combined approach was only applied to PAT methods. In addition, it was mentioned that challenges were experienced when combined approaches were not accepted by health authorities. One company mentioned that the combined approach was challenging for methods used for cell and gene therapies due to their inherent variability.

Platform Analytical Procedures

ICH Q2(R2) describes the use of platform analytical procedures for molecules that are sufficiently alike with respect to the attributes that the platform analytical procedure is intended to measure [1]. The survey asked several questions to respondents on their current and future use of platform analytical procedures.

Over 50% of respondents answered that they have utilized platform analytical procedures in clinical development (see Figure 5). However, slightly more than 10% have successfully been able to secure approval of platform analytical procedures with abbreviated

validation for commercial registration. When asked why companies had not been able to implement platform analytical procedures for commercial products, one respondent explained, the concept is "not implemented across entire agencies and for all modalities. [There is a] lack of understanding in health authorities and knowing what they are looking for."

Despite the current state, response to a follow-up question showed that those who are willing to implement for future commercial registrations increased to 45% (see Figure 5), a significant increase. However, only 10% responded that they will remain solely focused on clinical implementation for platform procedures (this response is not shown in the figure). Many analytical techniques were cited as having potential for implementation as platform analytical procedures, with the most commonly cited procedures used to analyze biologic products such as size-exclusion chromatography and cation-exchange chromatography.

Multivariate Analytical Procedures

Utilization of multivariate analytical procedures has grown significantly with the introduction of QbD in ICH Q8 over two decades ago [5]. The Concept Paper for ICH Q2(R2) and Q14 described that Q2 (R1) was not sufficient to demonstrate the suitability of multivariate methods and that the revision of Q2(R1) would include validation approaches for analytical procedures based on instrumentation that provides spectra across a frequency range [6].

In response to a survey question asking if the additional information provided on multivariate analytical procedures in ICH Q2(R2) and ICH Q14 provides greater clarity on what is expected for registration of these procedures, the majority (59%) of respondents think that additional information in Q2(R2) and Q14 on multivariate analytical procedures provides greater clarity for registration of these procedures. From written comments, respondents welcome a harmonized global standard for submission. Some respondents also pointed out that information in both guidelines remains relatively high level.

Real Time Release Testing (RTRT)

When asked if the additional information provided in ICH Q14 makes it more likely that their organization will implement RTRT, only 33% respondents agreed that additional information in the ICH Q14 guideline will lead to increased use of RTRT, and 32% disagreed. From written comments, respondents think that there is no clear incentive, and utilization of RTRT is mainly driven by product manufacturing requirements, control strategy, ICH Q13, and existing regional technical guidance. As one respondent put it, "We will use RTRT when it makes sense."

Analytical Procedures for Biological Products

The majority (54%) of the participants agreed that the additional information provided on analytical procedures for biological products in ICH Q2(R2) and ICH Q14 will have a positive impact on their review and approval process in the long run. Only 14% disagreed, while 7% did not respond, and 25% found the question not applicable. Comments were positive around the guideline's broad applicability to new modalities and complex technologies. Respondents were optimistic that a harmonized guideline would help to set a baseline of expectations, however, concerns were raised that broad acceptance by regulatory agencies might take a long time. Respondents also expressed concerns that more reviewer questions may result from the submission of information on complex topics such as design of experiments (DOEs).

Enhanced Approaches to Analytical Procedure Development

ICH Q14 describes enhanced approaches to analytical procedure development and introduces new regulatory tools for analytical procedure lifecycle management, which can enable post approval changes [2]. When participants were asked if their organizations were ready to implement these new approaches, 19% indicated that they were ready or had already implemented them. While this percentage is low, it was encouraging to see that 39% reported ongoing internal preparation activities for implementation.

When asked which elements of enhanced approaches or post approval change management tools that have been or will be implemented in analytical procedure development, respondents provided the information summarized in Figure 6.

Further insights into implementation challenges can be gained by examining individual elements more closely. For the elements of Analytical Target Profile (ATP), risk assessment, Design of Experiments (DOE), modeling, and analytical procedure control strategy, the reasons cited for lack of implementation or planning were highly consistent:

- Lack of global regulatory acceptance
- Lack of experience, subject matter exertise (SME), or training
- Increased cost

Two additional elements—Method Operable Design Region (MODR) and Established Conditions (ECs)—received significant feedback regarding why these have not been or will not be implemented. For MODR, respondents generally indicated that it offers very little value for lifecycle management re12%lative to the increased cost required to develop, validate, and maintain it. For ECs, the primary concern was lack of global regulatory acceptance. Respondents specifically noted that this concept was first introduced in Q12 [7], which reached Step 4 in 2019 but has yet to be implemented across all ICH regions. Additional concerns included lack of experience (SME), and increased cost.

The final topic in this section focused on the use of enhanced approaches to analytical procedure development, to better understand what types of procedures and what modalities were under consideration. Most of the responses indicated that chromatographic procedures were a primary focus area, with an additional mention of spectroscopic methods. As for modalities, the responses were broad and inclusive, covering both synthetic and biologic modalities, as well as combinations of the two.

Figure 6: Distribution of elements of enhanced approaches or post approval change management tools that have been or will be implemented in analytical procedure development. (Note: Percentages for each element are calculated based on the total number of responses.)

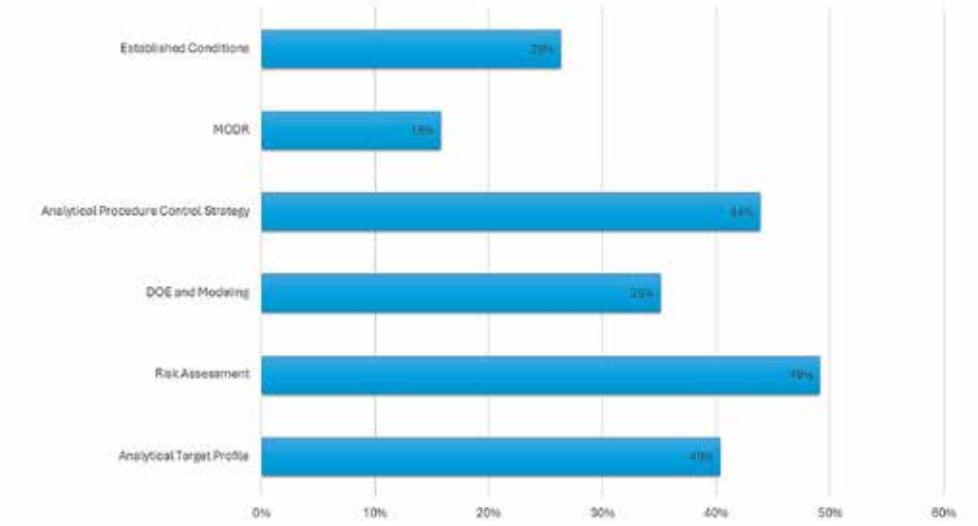
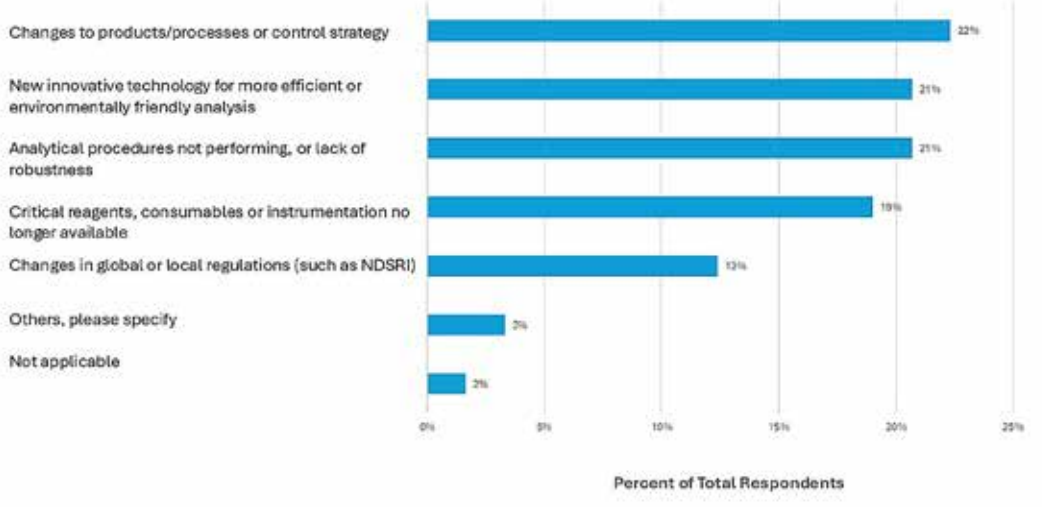


Figure 7: Major reasons for sponsors to make post-approval changes to analytical procedures (respondents were asked to select all that applied).



Regulatory Submission Experience

Respondents were asked if they had filed analytical procedures developed using enhanced approaches in commercial registrations. Only 12% responded affirmatively, while 56% stated they had not done so. The positive responses covered small molecule assay, impurity, and dissolution methods, as well as procedures for biologics submitted as part of a pilot program within the United States.

When asked whether development studies were described in commercial registrations, only 24% of respondents responded that either a development summary or details were provided (in addition to robustness studies). A summary of risk identification, justification of ECs, and description of performance characteristics and criteria were provided in one case, but several respondents acknowledged that details about method development—including elements of the enhanced approach—would need to be filed in the future once ICH Q14 adoption is more widespread.

Following initial submissions, sponsors may need to make post approval changes to analytical procedures. Potential drivers identified by respondents are presented in Figure 7. Additional feedback cited continual improvement considerations as well.

When asked whether analytical procedures had been filed in commercial registrations or post approval changes utilizing ICH Q12 lifecycle management concepts, only 11% of respondents indicated that they had done so. The types of analytical procedures included

those for biologics and small molecules. The Q12 tools utilized were Post Approval Change Management Protocols (PACMPs), Product Lifecycle Management (PLCM) documents, and the structured approach for post approval changes. Most submissions had been approved, primarily in the United States.

It is anticipated that applying principles described in ICH Q14 for analytical procedures can improve regulatory communication between industry and regulators and facilitate more efficient, scientifically sound, risk-based approval and post approval change management of analytical procedures. Approximately 50% of respondents cited examples where they would like to make changes to an analytical procedure but were hampered by regulatory constraints, as even minor changes require many regulatory approvals in multiple markets. This process is time-consuming and often necessitates duplicate testing, leading to significant supply chain impacts. In one comment, an analytical column was replaced due to failure, but the conditions were left unchanged due to the regulatory burden of achieving approval of the optimized procedure. In another comment, modernization of HPLC to UPLC systems (to shorten runtime and reduce environmental impact), or to switch from SDS-PAGE to capillary electrophoresis (CE), were not pursued due to perceived regulatory barriers.

When asked whether their company had a case study similar in format to the existing ICH Q14 case studies in Annex A—including elements such as the Analytical Target Profile (ATP), use of the enhanced approach to development, identification of Established Conditions (ECs), and implementation of a change—11 positive responses were received. Several respondents mentioned that they were in the process of filing with health authorities or intending to publish their case study.

In parallel with the survey described here, the ISPE PQLI Analytical Methods Strategy ICH Q2(R2)/Q14 team has described the challenges of analytical change management and how ICH Q14 concepts offer streamlining opportunities. (See Castle et al. article on page 30.)

DISCUSSION

The survey findings highlight the opportunities that pharmaceutical industry representatives identify in the finalization and adoption of ICH Q2(R2) and Q14. However, as with all incremental changes, challenges remain in implementing the guidelines and adapting to evolving regulatory expectations. In 2017, a survey was conducted by the IQ Consortium's Analytical Quality by Design Working Group focused on evaluating progress in analytical Quality by Design (QbD) [8]. While this effort predates the recent ICH revisions, it explored the use of Analytical Target Profiles (ATP), enhanced approaches to analytical procedure development, and regulatory experiences and outcomes from leveraging these options. In general, the majority of respondents had adopted some elements of analytical QbD approaches, but the potential of regulatory relief had not yet been realized.

One of the primary concerns raised in the current survey was the lack of global regulatory alignment regarding the acceptance of new strategies. Respondents expressed concern that some authorities may be hesitant to embrace platform analytical procedures and risk-based validation approaches, leading to inconsistencies in approval processes and potentially redundant work to meet expectations of different markets. Even when all ICH markets adopt these tools, there remains an opportunity for disharmony from non-ICH markets.

Concerns surrounding the ICH Q2(R2) requirements for assessing confidence intervals against corresponding criteria were commonly expressed. These concerns include uncertainty about setting criteria that will be deemed appropriate by a range of reviewers, the need for increased validation data required to meet statistical design requirements for more variable procedures or analytes, and a lack of internal statistical expertise to analyze and interpret the data. It is critical that industry and regulators converge on generally accepted practices for reporting confidence intervals in accuracy and precision studies to ensure meaningful and compliant implementation of this element of the guidance.

Companies expressed enthusiasm about ICH Q14's lifecycle management approach for post approval changes. However, many feel constrained by regulatory uncertainties surrounding the flexibility that could be gained through the use of enhanced development tools, such as the establishment of ATPs and MODRs.

Platform analytical procedures offer a promising avenue for efficiency gains. The ability to leverage existing data and prior knowledge across multiple products reduces redundancy in method validation and transfers [9]. However, full acceptance by health authorities remains a work in progress.

CONCLUSIONS

This survey provides valuable insights into the readiness and concerns of the pharmaceutical industry regarding the implementation of ICH Q2(R2) and Q14. Key takeaways include:

1. ICH Q2(R2) implementation presents challenges related to reporting requirements for confidence intervals, including the setting of meaningful acceptance criteria and the need for statistical expertise.
2. Significant opportunities exist in leveraging prior knowledge, platform methods, and enhanced validation strategies, and respondents are optimistic about implementing these tools.
3. Regulatory harmonization remains a key concern—particularly for platform analytical procedures and post approval changes—despite the availability of tools such as those presented in ICH Q12 [10]. Further implementation efforts are needed to ensure that global regulatory alignment on Q2(R2) and Q14 expectations.

Collaboration between companies, regulators, and industry organizations will be essential to ensuring a smooth and effective transition to these new guidelines. These efforts are already underway, with regulators and industry providing case studies and examples of successful implementations of new practices [11-14]. The findings presented here offer additional insights to direct future efforts toward areas of greatest impact and value.

Acknowledgements

The authors would like to acknowledge the ISPE Product Quality Lifecycle Implementation (PQLI) Analytical Methods Strategy (ICH Q2(R2)/Q14) technical team for its contributions to the subject matter discussed in this paper.

For more information about ISPE's PQLI, visit ispe.org/initiatives/pqli

References

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "Validation of Analytical Procedures Q2(R2)." Published November 2023. https://database.ich.org/sites/default/files/ICH_Q2%28R2%29_Guideline_2023_1130.pdf
2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "Analytical Procedure Development Q14." Published November 2023. https://database.ich.org/sites/default/files/ICH_Q14_Guideline_2023_1116_1.pdf
3. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "Validation of Analytical Procedures: Text and Methodology Q2(R1)." Published November 2005. https://database.ich.org/sites/default/files/Q2%28R1%29%20Guideline.pdf
4. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). (2025). "ICH Q2(R2)/Q14 Training Materials: Module 2 – Fundamental Principles of ICH Q2(R2)." 2025. https://database.ich.org/sites/default/files/ICH_Q2%28R2%29Q14_TrainingMat_Module%20_2_2025_0620.pdf
5. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "Pharmaceutical Development Q8(R2)." Published August 2009. https://database.ich.org/sites/default/files/Q8%28R2%29%20Guideline.pdf
6. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "Final Concept Paper ICH Q14: Analytical Procedure Development and Revision of Q2(R1) Analytical Validation." Published 2018. https://database.ich.org/sites/default/files/Q2R2-Q14_EWG_Concept_Paper.pdf
7. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management Q12." Published November 2019. https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf
8. Hewitt E, Rignall A, Trone MD, et al. "Evaluating progress in analytical quality by design." *Pharmaceutical Technology*. 2017;41(4). https://www.pharmtech.com/view/evaluating-progress-analytical-quality-design
9. Graul TW, Cauchon NS, Bernardoni F, et al. "Industry perspectives on practical application of platform analytical procedures." *Pharmaceutical Engineering*. 2024;44(5).
10. Zavialov E, Thomas A, Ramdas S, Ocheltree T, Langer C. "ICH Q12: A transformational product life-cycle management guideline." *Pharmaceutical Engineering*. 2020;40(3). https://ispe.org/pharmaceutical-engineering/may-june-2020/ich-q12-transformational-product-life-cycle-management
11. Kirkpatrick D, Gupta N, Gopalaswamy R, et al. "The role of enhanced analytical procedure development in facilitating post approval changes via established conditions." *The AAPS Journal*. 2025;27(61). https://doi.org/10.1208/s12248-025-01037-6

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BARRIERS TO INNOVATION IN PHARMACEUTICAL MANUFACTURING

Insights from Five Case Studies

By Roger Nosal, Nina Cauchon, PhD, David Churchward, Jean François Duliere, J. Paul Kirwan, PhD, John V. Lepore, PhD, Maurice Parlane, Christopher J. Potter, PhD, Alice Redmond, PhD, Greg Rullo, and Hirofumi Suzuki, PhD

In April 2023, ISPE launched a survey to understand the sources of barriers to technological innovation within the pharmaceutical industry. This survey is part of an expansive and significant initiative by ISPE, Enabling Global Pharma Innovation: Delivering for Patients, which aims to promote consistent and harmonized interpretation and implementation of guidelines issued by the International Council for Harmonisation (ICH). The overarching goal is to improve global patient access to innovative medicines and technologies.

The survey consisted of three parts: multiple choice questions focused on demographic and summary-level innovation experience; specific examples of innovation development experience, and expanded case descriptions. The results have been published on ISPE's regulatory webpage [1], fulfilling the third component of the initiative's first phase by presenting more specific information in case studies that illustrate innovation experience and associated challenges.

The purpose of this ISPE initiative is to understand the circumstances and confirm the contributing factors that can present barriers to innovation, including the specific origins, extent, and magnitude of challenges and barriers that limit and reduce the development and implementation of innovative technologies [2]. Although regulatory authorities globally have embraced technological innovation to improve product quality assurance, accelerate product development, reinforce supply chain reliability, and increase patient access to medicines, there are still economic and regulatory barriers that discourage the development and implementation of new, innovative technology globally.

In fact, several regulatory authorities—including the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the UK Medicines and Healthcare products Regulatory Agency (MHRA)—have actively promoted the adoption of innovative and advanced pharmaceutical manufacturing technology by introducing regulatory options that enable industry to develop and implement advanced manufacturing technologies. While it is incumbent on industry to modernize manufacturing processes to improve productivity and to strengthen confidence in product quality assurance, the conspicuous lack of global regulatory harmonization diminishes incentives for industry to invest in innovation, which indirectly limits access to safe, effective, and quality drug products to patients globally.

OVERVIEW OF CASE STUDIES

The five case studies described herein demonstrate individual company investments in new, innovative technologies that are designed for the manufacture of products intended for global markets. They also reflect the industry's enthusiasm to embrace the global regulatory challenges associated with implementation. While their specific experience and observations include a measure of success, particularly with respect to regulatory interactions, many challenges have been highlighted. These case studies reflect and exemplify findings from the ISPE survey, which include:

Regulatory Authorities

Interactions with multiple regulatory authorities take time and relatively large numbers of resources. Among regulatory authorities, the US FDA is considered the easiest to engage with because of its well-established Emerging Technology Program (ETP) and the Center of Biologics Evaluation and Research's (CBER) Advanced Technology Team (CATT) as well as its capacity to review and shepherd innovative proposals through the existing regulatory framework.

Industry Collaboration

While EU regulatory authorities are reluctant to discuss technological innovations without linking them to a specific product, which is considered a missed opportunity to enable and endorse platform technology. However, from time to time, they have entertained discussions about technological significance in the absence of specific product applications. This is an opportunity for regulatory authorities to reinforce the importance of collaborative engagements with industry by highlighting how they are working with industry to advance innovative technologies through the EMA's Quality Innovation Group (QIG), ETP/CATT. The QIG's Listen and Learn Focus Groups have been a welcome opportunity for engagement.

Duplicate and Redundant Manufacturing

There is concern with duplicate andredundant manufacturing and testing even after an innovation is approved in an application. Duplicative and redundant testing introduces unnecessary delays and increases resource demand. It has also been cited as a major barrier to investing in this new technology.

Transparency

Transparency of timelines for commercial implementation is necessary to fully realize productivity and return on investment (ROI) and it could be useful for regulatory engagement. Balancing the challenges associated with time constraints and resource requirements is particularly challenging in early research and development programs.

Innovative Technology

Innovative technology is typically intended to be global in scope even though it may be pursued and implemented incrementally from one region to another. For example, if global regulatory divergence dramatically increases the time and costs of developing customized applications for an innovative glass vial, that impact falls directly on patients and caregivers who will not benefit from reductions in broken vials that could result in drug shortages.

SUMMARY OF CASE STUDIES

Case Study 1: Azurra FAB

Case study 1 features a fully robotic aseptic filling line with mobile support robots (called "butler" robots). It is at an early phase whenrequests have been made to multiple regulatory authorities to introduce the concept. Due to high capital cost and long lead times, the concept has not been associated with any specific product; although, it should be widely applicable as a platform for aseptic products assembled into vials, syringes, and cartridges.

Thus far, only the US FDA has agreed to face-to-face discussions and accepted the concept into its Emerging Technology Program (ETP). The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom has provided written input and may interact and consult with the US FDA. The European Medicines Agency (EMA) and a specific member state's agency, Italy, have declined to discuss the project because it is not associated with any specific product. This indicates EU agencies are reluctant to discuss technology innovations without them linking to a specific product.

Table 1: Summary of case studies.

	CASE	DESCRIPTION
1	Azurra FAB	A fully robotic aseptic filling line with mobile support robots (called 'butler' robots)
2	Multi-Attribute Method (MAM)	A high-resolution, LC-MS-based, advanced peptide mapping analytical method designed to replace several current methods typically used for characterization and routine testing of biopharmaceutical products
3	Maholo Robotic Cell Culture Automation System	An adaptable cell culture automation system that can perform a series of cell culture operations, i.e., cell seeding, media change, passaging and harvest, etc. without human intervention
4	Application of Process Systems Modelling for Pharmaceutical Process Development and Manufacturing	A platform technology for process control strategy and design including use of digital twins and hybrid models
5	Valor® Glass	An alternative borosilicate glass vial that effectively reduces breakage and improves productivity, product quality assurance and supply chain reliability

CASE STUDY 2: MULTI-ATTRIBUTE METHOD

Case study 2 describes the adoption of the Multi-Attribute Method (MAM): a high-resolution, liquid chromatography/mass spectrometry (LC-MS)-based advanced peptide mapping analytical method designed to replace at least 4 methods typically used for characterization and routine testing of biopharmaceutical products. One product was selected for this project starting at the early clinical stage. This was a complex and resource-consuming project that required qualification, validation and compariison with existing methods.

The project was risk reduced by engagement with multiple health authorities, i.e., US FDA, Japan Pharmaceuticals and Medical Devices Agency (PMDA), and China National Medical Products Administration (NMPA) (formerly CFDA). This included direct meetings as well as iterative exchanges of information. The project was accepted into the US FDA ETP (because the CATT and QIG were not established when the innovation was initially proposed). The

sponsor has received health authority approval or "safe to proceed" for clinical trial applications in 32 countries, including harmonized criteria with respect to MAM.

During clinical development, the US FDA requested that the company maintain side-by-side testing of MAM and conventional methods for an extended period, This was despite extensive characterization data submitted for agency review. Side-by-side testing is resource intensive, undermines the impact of innovative approaches, and discourages industry investment in emerging technologies.

CASE STUDY 3: MAHOLO ROBOTIC CELL CULTURE AUTOMATION SYSTEM

Case study 3 focused on Maholo, a unique, novel, and adaptable humanoid dual arm robotic system that can perform a series of cell culture operations, including cell seeding, media change, passaging, and harvesting. By precisely and consistently manipulating peripheral equipment (i.e., centrifuge, microscope, digital pipettes, cell counter, refrigerator, and CO_2 incubator) within an unmanned environment, similar to or better than a skilled human operator. The system can also perform a series of cell culture operations. Maholo is intended to be implemented as a platform technology that has yet to be introduced for a product application.

Interactions with EMA QIG were timely and productive providing positive and supportive feedback on appropriate cGMP necessary for robotic automation as well as potential use with AI technologies. Considering this automation for highly selective gene and cell therapies significantly reduces human intervention and the potential risk for quality issues, the company is concerned that demand for comparability data will be required during the discussion of automation, which may pose a challenge. In addition, there will likely be divergent regulatory expectations for the implementation of this innovation globally. Therefore, it is important for major regulatory authorities and the pharmaceutical industry to actively promote and communicate future-oriented technology development and opinion consolidation. This is the entire pharmaceutical industry can progress towards innovative technology development for the benefit of patients.

CASE STUDY 4: APPLICATION OF PROCESS SYSTEMS MODELING FOR PHARMACEUTICAL PROCESS DEVELOPMENT AND MANUFACTURING

Case study 4 involved platform technology for process control strategy and design, including the use of digital twins and hybrid models.

While there are limited precedents and experience using model-based approaches for low-to moderate- risk product developments, the current intent is to focus on postmarketing applications for process control using digital twins and hybrid models (mechanistic and empirical) as a platform for a broad portfolio of products. These models improve process efficiency, product quality, use of prior knowledge, speed of development, and commercialization.

As such, for some well-established mechanistic "low-impact" models, development and implementation timelines are relatively short (1 to 2 years). For complex models and applications, current estimates are 5 tos7 years for development and initial commercial implementation. Timelines for subsequent deployment should be significantly improved; however, this is highly dependent on the initial success of the leading program.

Midway through the development stage, engagement with the US FDA and EMA through formal meetings served primarily as an opportunity to share information. Engagement with the EMA QIG was highly effective and led to substantive feedback that was then directly reflected in the "Preliminary QIG Considerations regarding Pharmaceutical Process Models" published by the Quality Innovation Group (QIG) of the European Medicines Agency (EMA). While no engagement with the US FDA ETP, the QIG is sharing information with the US FDA and PMDA on this subject area. Establishing a path for joint or parallel scientific input on emerging technologies across multiple major regulatory authorities would enable and expedite implementation of innovation.

CASE STUDY 5: VALOR® GLASS

Case study 5 featured an alternative borosilicate glass vial that effectively reduces breakage and improves productivity, product quality assurance, and supply chain reliability.

Valor®™ glass is an innovative glass vial substitute/replacement for Type 1 (USP) borosilicate glass vials. It is composed of elements used in Type I borosilicate containers (e.g., silica, alumina, etc.) with a boron-free formulation. This formulation eliminates delamination, improves overall extractables and leachables performance and eliminates in-line breakage that routinely results in product contamination and loss, disruptive and delayed manufacturing and drug shortages. The use of this innovative glass effectively improves productivity, product quality assurance and supply chain reliability. In addition, it reduces the potential for glass vials breaking during shipping, at pharmacies, hospitals, care centers, and in patients' homes.

The innovative glass vials were intended to be implemented as a platform replacement for an entire portfolio of innovative, approved, and generic products. Essential "DOE" risk assessment of the 75 products targeted for implementation was developed to demonstrate comparability/equivalence for each category of product families, which would limit the need to perform a complete battery of tests, including developing stability data on every product.

Interactions with the US FDA Emerging Technology Team (ETT), part of the ETP, were productive and largely supported the initial proposal to identify the appropriate sets of critical quality attributes that are representative of different categories of drug products and to develop an analytical strategy to demonstrate comparability and equivalence for each category of product families (the QIG and CATT were not established when the innovation was initially proposed). However, subsequent engagement with representative assessors from the US FDA triggered a relatively conservative response at the time of regulatory submission.

As a result, the regulatory strategy was revised to incorporate

several additional criteria and an expectation that stability results for all 75 products within the product family would accompany all post approval applications. This significantly increased the duration for implementation. Despite compelling comparative data provided by the glass vial manufacturer, the US FDA assessors remained concerned with "show us the product data" rather than extrapolating platform data. This experience is an example of the challenges of being the first to come forth with new technology.

The outcome was, for the US applications, a qualified success in that a measure of regulatory flexibility and reduced timelines for implementation was considered feasible, though the potential for maximum benefit was not realized.

CONCLUSION

In general, these case studies provide, confirm, and amplify the results from the recently published ISPE report, "ISPE Global Pharmaceutical Innovation Survey Findings: A Review [1]" which examines barriers to innovation. In general, return on investment is a critical factor in decisions regarding development and implementation of innovative technologies. Observations from these case studies indicate that even at the early stage of evaluating an innovation, global regulatory divergence is a consideration with an associated cost. Each case study projected that regulatory reliance and alignment among regulatory authorities could effectively offset the investment risk, and could facilitate global implementation of innovative technologies.

APPENDIX

Case Study 1: Azurra FAB

Project description

The innovative Azzurra FAB is a fully robotic aseptic filling line with mobile support robots (called "butler" robots). Several regulatory agencies are aware of the new innovation, so there is not an issue with ISPE sharing this information with other agencies. The purpose of this project, and the genesis of the Azzurra FAB, is to overcome the many current challenges with the existing aseptic filling technology; such as long lead times, high capital equipment costs and the extensive use of gloves at commercial scale. The intent is to deliver a paradigm shift in drug product manufacturing facility design and operation.

- The primary business drivers for the innovation were cost, lead time and a more robust quality solution that eliminates the risk of human interaction.
- The decision to proceed with the development and implementation of innovative technology was based on the challenges of long lead times and high costs with limited standardization experienced during the COVID-19 pandemic.
- The innovative technology was not developed with a specific product application or a post approval change/supplement.
- The innovation is intended as a platform for a range of product portfolios containing vials, syringes and cartridges.
- The development of the Azzurra FAB is ongoing, based on feedback from regulatory agencies, with some degree of complexity when removing the need for human interaction.
- The concept of the Azzurra FAB, including the collaborative approach with industry and regulatory agencies, has been presented at ISPE conferences in Asia, Europe and the US with some positive and encouraging feedback.

Engagement with regulatory authorities

- The MHRA, the US FDA, and the EMA were approached prior to the implementation of the Azzurra FAB in July 2023.
- The Azzurra FAB was accepted into the US FDA Emerging Technology Program (ETP) in October 2023 with an initial meeting with the ETT in January 2024.
- The MHRA provided a written response to on questions submitted to the Innovation Office November 2023. The MHRA was invited to the US FDA meeting in January 2024 and initially accepted the invitation but then had to decline at the last minute due to conflicting priorities.
- When it was clear the EMA Quality Innovation Group (QIG) was not going to respond to the application, an application was made via the local Italian Medicines Agency (AIFA) Innovation and Scientific Advice Office in March 2024. AIFA responded in April 2024 declining the opportunity to meet due to there not being a specific product to review as part of the application. AIFA instead decided the alternative scientific advice procedure would be a more appropriate route.
- The respective regulatory authorities have not issued approvals for the Azzurra FAB due to the continued development of the innovative technology.
- There have been no pre-approval inspections triggered by the innovative technology applications due to the continued development of the innovation technology and no specific products selected.
- The EMA and AIFA do not seem to be receptive to innovative technologies that do not come with a specific product to review. This is definitely a barrier to innovative technologies when trying to obtain feedback and support during the early stages of development. Fortunately, the MHRA and the US FDA are more forward thinking and understand the need for early engagement and support. The US FDA Emerging Technology Program (ETP) in particular seems to be the most advanced and effective program in this respect based on the interaction with several different agencies.

Opportunities and challenges

- For future innovative technologies, there is a reluctance to engage the EMA and instead to focus on other regulatory authorities.
- The EMA could adopt the same or similar approach as the US FDA by supporting and encouraging innovative technologies with or without a specific product. The EMA's position represents a missed opportunity that will not help develop and promote innovative technologies that have the potential to drive significant opportunities.

Case Study 2: The Multi-Attribute Method

Project description

Case study 2 involved method development and regulatory acceptance of the multi-attribute method (MAM): a high-resolution, LC-MS-based, advanced peptide mapping method [3-6]. The business drivers for this innovation included increasing the efficiency of drug substance and drug product release testing, and the introduction of an advanced analytical capability. The decision to proceed with development and implementation of MAM was driven by potential resource savings due to increased testing efficiency and a reduced number of test methods on the specification.

- MAM was filed as a new product application in clinical trial applications continuing through phase 2.
- It was intended for widespread use across the company portfolio, but one program was used to establish a regulatory precedent.
- The timeline for the project was driven by the goal of regulatory acceptance of MAM for the replacement of conventional methods.
- The level of complexity was high, with extensive characterization, side-by-side testing, and detailed method qualification performed to support the replacement of conventional methods with MAM.
- The project is viewed as a success with further assessment on-going.

Engagement with regulatory authorities

- The company applied to and was accepted into the US FDA CDER Emerging Technology Program (ETP).
- It met with the US FDA on multiple occasions during clinical development, including on-site.
- The company submitted extensive characterization data using MAM for Agency review, and it responded to written requests for information.
- Besides the US FDA, the company engaged with other global health authorities (including Japan's PMDA and China's National Medical Products Administration (NMPA) (formerly CFDA) through written correspondence and presentations intended to promote awareness of MAM and provide information on development.
- The interactions included direct meetings as well as iterative exchanges of information. The meetings and exchanges of information were very productive and health authorities, particularly the US FDA, provided significant feedback.
- To date, the company has received health authority approval or "safe to proceed," including harmonized criteria with respect to the MAM for clinical trial applications, in 32 countries: : Argentina, Austria, Belgium, Bulgaria, Canada, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Greece, Honk Kong, Hungary, Italy, Japan, Korea, Latvia, Mexico, Netherlands, Poland, Romania, Russian Federation, Slovakia, South Africa, Spain, Switzerland, Taiwan, Turkey, Ukraine, United States.
- The process was extremely time and resource intensive. During clinical development, the US FDA requested that the company maintain side-by-side testing of MAM and conventional methods for an extended period of time, despite extensive characterization data submitted for agency review.
- Side-by-side testing is resource intensive, undermines the impact of innovative approaches, and discourages industry investment in emerging technologies.

Opportunities and challenges

- Establishing clinical trial application approvals for the precedent product took significant time and resources, especially with the expectation of side-by-side testing with the MAM and conventional methods, which was discouraging from a business perspective.
- Establishing clear near-term and long-term goals with a well-defined scope is recommended. In general, maximizing cross-functional alignment internally on the overall strategy and objectives for an innovative technology will improve and expedite the regulatory strategy globally. Based on the company's experience, no changes to the approach for application to regulatory authorities were warranted.
- Enabling innovation significantly depends on global harmonization among health authorities to offset the business risk. If a technology is accepted in some jurisdictions but not in others, a company is forced to maintain the GMP and regulatory status of both conventional and innovative technologies, which is resource intensive.
- Global regulatory reliance and harmonization will enable and de-risk adoption of innovative technology and encourage industry investment in modernization. Early collaboration amongst regulators to evaluate new technology should be encouraged to speed up the process. Successful global harmonization depends on industry commitment as well as regulatory authority acceptance.
- Industry should ideally support the concept of a single, global dossier, so as not to generate extensive variant submissions (e.g., with redactions for some jurisdictions) based on differing current regulatory expectations. This is difficult to do because the current regulatory expectations for new technology, including the data requirements for submission, are widely divergent.

Case Study 3: Maholo Robotic Cell Culture Automation System

Project description

Maholo is a unique and novel robotic system that can perform a series of cell culture operations consistently and precisely, similar to or better than a skilled human operator. This allows for manipulation of peripheral equipment within an unmanned environment. It is an adaptable cell culture automation system developed by Robotic Biology Institute Inc., Japan. Maholo consists of a dual-arm humanoid robot and equipment necessary for cell culture, including centrifuge, microscope, digital pipettes, cell counter, refrigerator, and CO_2 incubator. The system can perform a series of cell culture operations, such as cell seeding, media change, and passaging and harvest, with a flexible scheduling and without human intervention (i.e., higher process consistency, reproducibility).

Cell therapy manufacturing faces challenges with process consistency, extremely high cost of goods, and dependence on highly skilled operators for manual process operations. This makes it difficult to reproduce and transfer complex processing steps including an operator's motion. The replacement of human operators with Maholo will dramatically reduce the need for human

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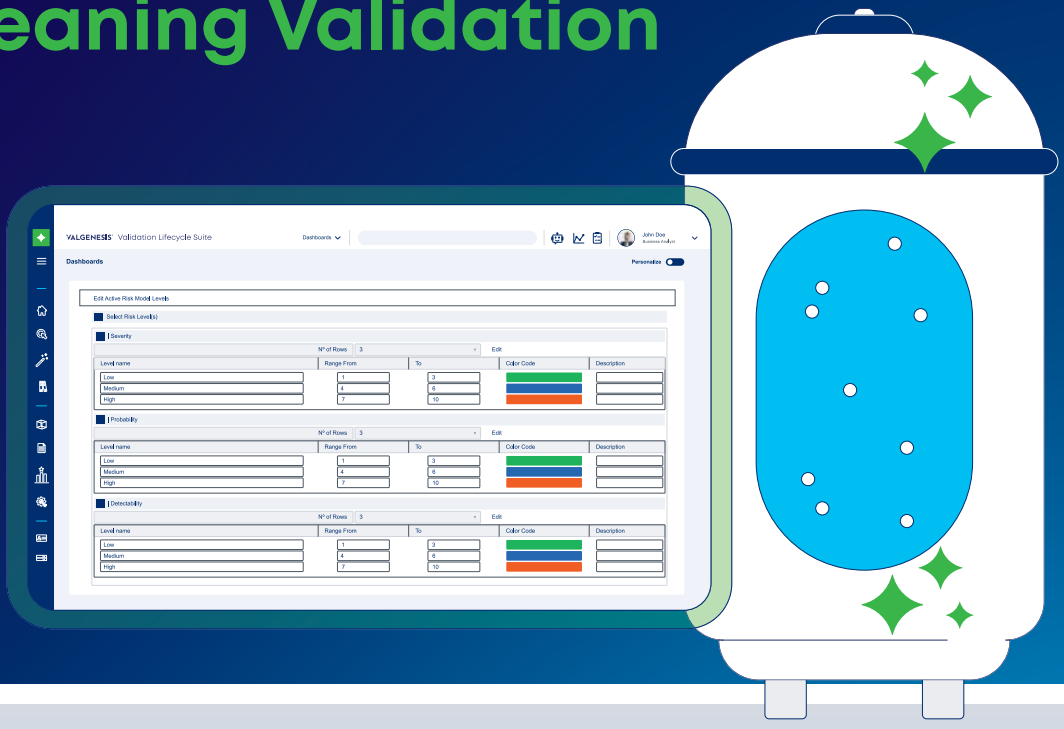

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intervention and thus reduce human error, leading to improved process consistency and decreased cost of goods.

Both the authorities and the industry understand the necessity of automation in the field of regenerative medicine, but there are many challenges that have hindered its progress. Because Maholo is skilled at imitating humans, it can cover everything from research to manufacturing on a single platform. Therefore, it can ensure consistency in development acceleration and quality assurance.

- The challenges and motivations for business arise from the complexity and difficulty of controlling cell-based products, resulting in long development periods and high development costs. The current manual processes that rely on existing know-how are not sustainable for future commercial manufacturing.
- Compared to traditional cell culture automation systems, Maholo can replicate cell culture processing with dual arms and 15-axis construction that (i) flexibly performs delicate cellular differentiation process, (ii) does not require complicated technology transfer, and (iii) enables design and performance of a simple, versatile and sustainable automation system, including use of Maholo software with minimal process-specific optimization of parameters.
- Cellular differentiation process from stem cell starting material requires highly skilled, often complex, and sensitive manual operations within a desired timeframe. Maholo can handle multiple culture procedures suitably and flexibly with highly precise, digitally controlled, sub-millimeter-scale arm motion.
- Maholo can imitate human operations using its dual arms, thereby minimizing process development. This means that a process developed with human operators can easily be translated to an automated process performed by Maholo. Once an operational motion by Maholo is created, the motion is saved and becomes transferrable digital data. Therefore, manual process steps do not require specific process transfer routinely required for training and qualification of human operators. This leads to reduced risk of human error and operational failure during process development and process technology transfer.
- General closed equipment and conventional automation systems are typically "custom" designed for specific/targeted products and are often limited with respect to broad applications and use. Additionally, for GMP manufacturing, conventional automation systems require "locking" manufacturing processes and then conducting a detailed, customized, design for hardware use. This approach is often not feasible for cell therapy products, especially in the early development stage. With the Maholo system, a customized hardware design is not necessary and operators can simply generate culture processes by combining commands of motions.
- Improvement in the rate of cell production will clearly reduce the manufacturing cost. The process was digitally made for the automation and will contribute to the reduction of technical transfer from research to manufacturing. This leads to shortening the development period for cell therapy. In addition to the return on investment (ROI) at the device level, this platform is being developed taking into consideration various related investment effects. This includesdevelopment acceleration and mitigation of potential quality risks, as it serves as a consistent platform connecting research to production.
- Maholo is intended to be implemented as a platform technology. If this platform is realized, it is expected to contribute to the acceleration development timelines and expand the product portfolio including improvement of the success rate of seeds that might be previously be terminated due to tech-transfer issues.

Engagement with regulatory authorities

- The EMA QIG and the US FDA CATT meetings were granted and conducted. It is acknowledged that both authorities have strong interest on this type of technology and digital innovations.
- Interactions with the EMA QIG were timely and productive. They provided positive and supportive feedback on the facility design and GMP understanding regarding utilization of robotic automationand Maholo's potential use with AI technologies. Interactions with the US FDA CATT were more educational and informative and helped to improve their understanding. Although limited resources were used to engage the US FDA, the firm had expected and hoped for more specific feedback from the US FDA CATT.

Opportunities and challenges

- Although the discussion is ongoing, in the field of regenerative medicine, there is often a demand to provide comparability data through process changes. We are concerned that similar data and opinions will be required during the discussion of automation.
- It is necessary to proceed with innovative new technologies, even in the absence of sufficient knowledge within the company, the pharmaceutical industry, and regulatory authorities. To obtain understanding and support for internal activities and the application of development themes, we would like to proceed in a manner that allows us to utilize the advice and collaboration of the pharmaceutical industry and regulatory authorities.
- Patients waiting for medicines and treatments exist all over the world, so ideally, they expect this type of innovative technology to be developed globally and promptly. However, due to the current state of regulatory affairs, it is anticipated that opinions may differ by region, which can also cause delays. Therefore, it is important for major regulatory authorities and the pharmaceutical industry globally to actively promote and communicate future-oriented technology development and opinion consolidation, so that the entire pharmaceutical industry can progress towards innovative technology development for the benefit of patients.

Case Study 4: Application of Process Systems Modelling for Pharmaceutical Process Development and Manufacturing

Project description

The primary business drivers for this innovation are improvements in process efficiency, product quality, use of prior knowledge, speed of development and commercialization.

- The organization has estimates of the benefits from a ROI standpoint, however, there is broad awareness that these targets are significant approximations that are subject to technical challenges and the external landscape (i.e., barriers to commercialization globally). It is too early to be able to provide specific breakdowns of business metrics for this broader initiative.
- For process model-based development studies, the company has implemented in limited cases for initial marketing applications. For process control schemes, the company has experience with commercial filings for continuous manufacturing (CM). However, there has not been a broader implementation for other commercial programs. The company's current intent is to focus on post-marketing applications for process control using digital twins and hybrid models (mechanistic and empirical).
- There is a long-term understanding that successful use of this technology would open the doors for greater platform application, particularly across a given modality (e.g., monoclonal antibodies or oligonucleotides). This could lead to very significant application across the company's portfolio (likelihood >50%).
- This area of focus is more of a portfolio of applications broadly comprised under "process modeling." As such, for some well-established mechanistic models being applied for development (i.e., "low impact" models), the development and implementation timelines are quite short (1 to 2 years). For the more complex models and applications, current estimates are on the order of 5 to 7 years for development and initial commercial implementation. The timelines for subsequent deployment should be significantly improved. However, this is highly dependent on the initial success of the leading program.
- The company has already had numerous successful deployments of process models for "low-impact" applications (i.e., process and control strategy design, process monitoring and operator training applications). For higher impact models, it is still too early to make a conclusion on the overall success of the initiative.

Engagement with regulatory authorities

- At mid-stage development, there was engagement with the US FDA and the EMA, both through formal meetings (e.g., project type C in the US) or by other paths (e.g., QIG Listen and Learn (L&L)/closed-door interactions focused meetings of the EMA's QIG).
- The project was accepted by the EMA QIG. We have not formally applied for entry into the US FDA ETP, but have kept the US FDA informed through the QIG, as they are sharing information on this subject area.
- The EMA QIG is a very promising vehicle for interaction. The listen and learn forums are effective at pulling in regulators outside of the EU (e.g., PMDA, US FDA) to ensure general awareness and current industry pain points. Closed door interactions with the QIG were highly effective and led to substantive feedback that was then directly reflected in a published EMA concept paper.
- For medium- and high- impact models other than CM, approvals have not been received or requested for Pre-Approval Inspections (PAIs) for our innovative technology applications.
- While no excessive requests have been received from regulatory authorities, there is some awareness that interpretations on GMP may play a role in divergent requests for Pharmaceutical Quality System (PQS) documentation on audits for low and medium impact models.

Opportunities and challenges

- The commercialization roadmap could be more well-defined in advance, with specific time points for regulatory engagement. This is an industry-wide challenge, with earlier research and development programs and there is always difficulty balancing the degree of timeline and project management with the resource requirements.
- It seems more likely that companies will need to have some regulatory staff to serve as emerging technology liaisons to regulators to maximize the use of the growing repertoire of regulatory tools authorities are offering. In addition, the ability to shepherd the technology through the regulatory process early on will greatly improve the success rate and timelines for successful implementation.
- A key area here is to establish a path for joint or parallel scientific input on emerging technologies across multiple major regulatory agencies. There appears to be some potential for International Coalition of Medicines Regulatory Authorities (ICMRA) to act in this capacity.
- It is often a challenge for industry to balance the need for early regulatory engagement with the overall odds of success within the organization. There is a strong desire to avoid wasting regulators time with projects that have a low likelihood of success. Some of this risk is mitigated by external joint working groups, such as ISPE, where a broader industry agreement on priority can trigger broader engagement with regulators on a specific area of technology.

Case Study 5: Valor® Glass

Project description

Case study 5 featured innovative glass vial substitute/replacement for Type 1 (USP/Ph. Eur.) borosilicate glass vials that significantly reduce\s in-line breakage that routinely results in product contamination and loss and disruptive and delayed manufacturing. The use of this innovative glass can significantly reduce drug shortages.

The innovative glass vials are composed of a proprietary, tempered aluminum/boron borosilicate and coating that imparts increased tensile strength to withstand product fill, lyophilzation, capping, and sealing. The composition of Valor®® glass maintains a glass network of elements used in type I borosilicate containers e.g., silica, alumina with a boron-free formulation that eliminates delamination and improves overall extractables and leachables performance. The use of this innovative glass will effectively improve productivity, product quality assurance and supply chain reliability. In addition, this innovative glass will reduce potential for glass vials breaking during shipping, at pharmacies, hospitals, care centers, and in patients' homes.

- The primary business drivers for the innovation were improved productivity and reduced manufacturing and inventory costs, improved quality assurance, and increased supply chain reliability and patient access.
- The estimated ROI was projected based on short-term adoption and implementation for more than 75 approved innovative and generic small molecule products (see Table 1) and long-term introduction for several innovative small and large molecule products including vaccines. Several anticipated cost savings factored over 5 years were generally estimated.
- The innovative technology was submitted as post approval supplements for approved innovative, and generic products.
- The innovative glass vials were intended to be implemented as a platform replacement for an entire portfolio of innovative, approved and generic products. An essential Design of Experiments (DOE) of the critical attributes representing the 75 products, where extreme, functional categories, reflecting different chemistry, pHs, buffers, etc., was the basis for assessment. Five conditional categories were identified, and extreme representative products were selected from each category family and evaluated under accelerated and extended stability conditions. This approach provided the context and basis for demonstrating equivalence for all other products within each category family to be able to justify applications for CB30s with 3 months of stability data.
- The original anticipated timeline from development of data to demonstrate product comparability and\/equivalence in the innovative vials to actual approval of the first application was approximately 1.4 years and approval of applications for all 75 products was approximately 2 years. This estimate was based on an approach that relied on identifying the appropriate sets of critical quality attributes that are representative of different categories of drug products and developing an analytical strategy to demonstrate comparability and equivalence for each category of product families. The primary goal was to be able to demonstrate comparability and equivalence for each category of product families that would limit the need to perform a complete battery of tests, including developing stability data on every product.
- Science- and risk-based approaches were used to demonstrate application of a platform technology for significant reduction in data requirements and application submission categories. The outcome was, for the US applications, a qualified success in that it allowed for a measure of regulatory flexibility and reduced timelines for implementation.

Engagement with regulatory authorities

- US FDA ETT was engaged through a formal application once the proposed post approval regulatory strategy to develop and implement the platform innovation for multiple products was established and endorsed by multiple internal disciplines. The cross-disciplinary team met with the US FDA ETT initially to present the technical and regulatory approach and subsequently with a team from the US FDA that was represented by several assessors from the Office of Pharmaceutical Quality and representatives from the Office of Generic Products. Additional interactions with specific regulatory assessors were engaged prior to submitting applications.
- The US FDA and EU EMA were contacted. The QIG was not in place at the time this innovation was being developed. At least two interactions with the US FDA were direct, whereas several others were iterative. The primary interaction with EMA Quality Working Party was direct and no further interactions were required thereafter as the EMA largely accepted the proposed regulatory strategy.
- The US FDA ETT accepted the application for innovative technology. The CATT and QIG were not established when the innovation was initially proposed.
- Interactions with the US FDA ETT were productive and largely supported the initial proposal to identify the appropriate sets of critical quality attributes that are representative of different categories of drug products and develop an analytical strategy to demonstrate. The ETT supported, in principal, the plan to demonstrate comparability and equivalence for each category of product families that would limit the need to perform a complete battery of tests, including developing stability data on every product. The US FDA agreed to the proposed 5 product category family equivalence assessments.
- However, subsequent engagement with representative assessors from the Office of Generic Products triggered a relatively conservative response. As a result, although less than normal stability data was required, the regulatory strategy was revised to incorporate several additional criteria. This included an expectation that stability results for all 75 products would accompany all post approval applications. This significantly increased the duration and resource capacity for implementation. From the company perspective, scientific rationale and risk assessments indicated the additional data was unnecessary relative to the risks associated with the vial replacement. In particular, the need to demonstrate appropriate and adequate stability for every product could have been achieved for most products within a family of products through a stability commitment in accordance with the approved stability protocol criteria.

Table 1: Projected savings for 75 products over five years.

Savings Areas	Outcomes	Estimated Savings (US$Milllions)
Product Integrity	No product loss because of broken vials	~17.5
Manufacturing Productivity	No disruptions in manufacturing schedules or delays dues to potential contamination	~36.3
Inventory Control	No disruption of inventory supplies	~2.1
Customer Satisfaction	No broken vials provide assurance of product reliability and continuity	~8.8
Total estimated savings (75 products/5 years)		~64.7

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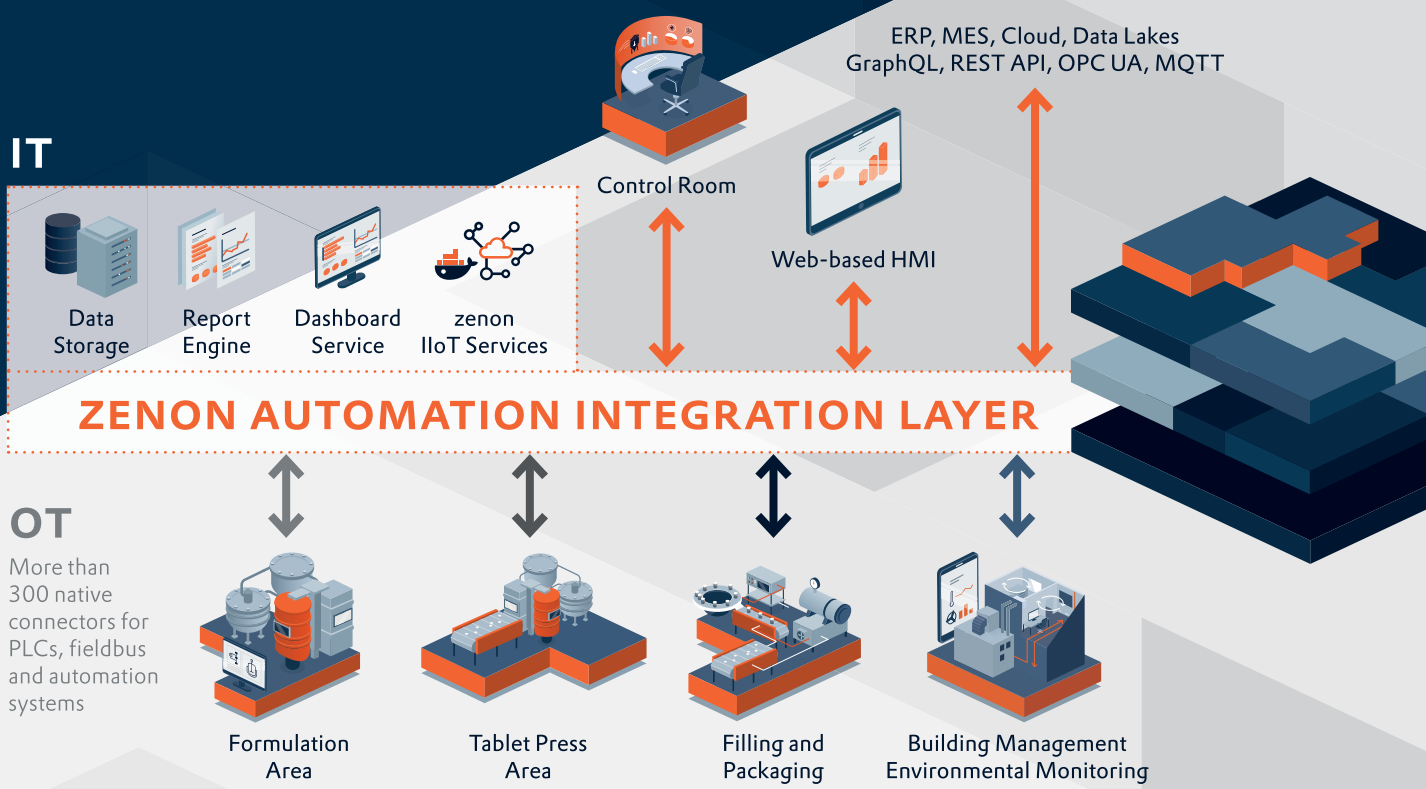

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Opportunities and challenges

- The data for the new glass compared to borosilicate was compelling. Under all comparability conditions, the innovative glass vial and the traditional USP Type 1 borosilicate glass vials are superior. The importance of that comparative data provided by the glass vial manufacturer was not taken into consideration scientifically, as the US FDA wanted to see the product data and a demonstrated zero risk. This experience is a prime example of the challenges of being the first to come forth with new technology.
- An assessment of regulatory requirements in other regions indicated that additional studies and expectations would be required beyond those indicated by the US FDA. As a result, the approval timing for subsequent applications were incrementally scheduled over several years to avoid inventory management complexity.

CONCLUSION

ISPE's Enabling Global Pharmaceutical Innovation Initiative encompasses a broad spectrum of advancements, including technical innovations in pharmaceutical manufacturing and analytical technologies, the introduction of new medical modalities, novel delivery and administration methods, and digital transformation through Pharma 4.0™. The initiative aims to enhance product quality assurance, ensure consistent and reliable supply, improve product usability, and expedite global patient access to innovative therapies. Where applicable, it also supports improved productivity and reduced manufacturing costs.

The scope of pivotal objectives for this initiative include:

- Contemporize manufacturing technologies, i.e., advanced modeling and simulation digitalized technologies
- Reinforce globally harmonized interpretation and implementation of ICH guidelines necessary to advance innovative technology and industry approaches such as Pharma 4.0™, establishing criteria for a globally accepted drug product control strategy
- Identify sources of regulatory challenges that are barriers or create limitations in applicability across multiple therapeutic modalities
- Increase the level of clarity and consistency in harmonized approaches and identify and promote incentives for implementation of innovative technology
- Leverage relevant regulatory harmonization initiatives and convergent regulatory approaches in progress regionally, accelerate adoption and implementation of ICH guidelines and other harmonization proposals, i.e., mutual recognition/reliance, ACCESS Work sharing, WHO, etc.
- Identify incentives for regulatory authorities to collaborate
- Assess learnings from the COVID-19 pandemic global regulatory and supply distribution experience that can serve as a roadmap, i.e., mutual reliance, parallel development, regulator engagement.

References

1. International Society for Pharmaceutical Engineering. "Enabling Pharmaceutical Innovation: A Report on the Barriers to Innovations Survey." April 2024. https://shorturl.at/v1pXC
2. Potter, C. "ISPE Global Pharmaceutical Innovation Survey Findings: A Review." *Pharmaceutical Engineering* 44, no. 6 (September/October 2024):60–6.
3. Kirwan, P. J. "The Multi-Attribute Method: Progression of Advanced Analytical Technology Through the FDA Emerging Technology Program, FDA Convening on Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches." Duke-Margolis Institute for Health Policy. 8 June 2023. Washington, D.C.
4. Rogers, R. S., M. Abernathy, D. D. Richardson, J. C. Rouse, J. B. Sperry, P. Swann, et al. "A View on the Importance of 'Multi-Attribute Method' for Measuring Purity of Biopharmaceuticals and Improving Overall Control Strategy." *AAPS Journal* 20, no. 1 (2017):7. doi:10.1208/s12248-017-0168-3
5. Rogers, R. S., N. S. Nightlinger, B. Livingston, P. Campbell, R. Bailey, R., and A. Balland. "Development of a Quantitative Mass Spectrometry Multi-Attribute Method for Characterization, Quality Control Testing and Disposition of Biologics." *mAbs* 7, no. 5 (2015):881–90. doi:10.1080/19420862.2015.1069454
6. Ren, D., G. D. Pipes, D. Liu, L.-Y. Shih, A. C. Nichols, M. J. Treuheit, et al. "An Improved Trypsin Digestion Method Minimizes Digestion-Induced Modifications on Proteins." *Analytical Biochemistry* 392, no. 1 (2009):12–21. doi:10.1016/j.ab.2009.05.018

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BALANCES AND SCALES

Metrology and Fitness for Intended Use

By Klaus Fritsch, PhD

Defining requirements for calibration and routine testing of weighing equipment in the laboratory and production remains a complex endeavor for pharmaceutical companies. Applying sound, risk-based metrological strategies across the entire pharmaceutical value chain will help manufacturers ensure compliance, consumer safety, and commercial success.

Accurate weighing is key to pharmaceutical quality control (QC). While pharmacopeias have begun to set clear metrological rules for QC weighing, a lack of guidance remains for weighing in production. This can complicate the definition of weighing requirements that are commensurate with the quality attributes of an API or finished pharmaceutical product.

However, new regulations, along with established weighing standards, are helping to close these gaps in practice. Consequently, outdated concepts such as the daily balance check and the idea that weighing a test load without stating the associated measurnonement uncertainty constitutes calibration can be substituted with state-of-the-art, risk-based assessments. This should help steer the industry toward risk-based quality management built on proven metrology.

The recent emphasis that pharmacopeias are placing on metrologically sound requirements for assessing balances used for analytical purposes will help move this process forward, with as-found and as-left calibration embedded as a cornerstone of a holistic performance verification strategy.

These risk-based strategies should also be applied to weighing applications in production. While weighing requirements for manufacturing are not under pharmacopeial jurisdiction, fostering consistency across the industry will help assure the accuracy that is paramount for regulatory compliance, consumer safety, and commercial success.

INTRODUCTION

Weighing is one of the key activities carried out in every quality control (QC) laboratory. Usually, it is one of the first steps in a whole analysis chain, e.g. when a sample or a standard is prepared for subsequent dilution and High-Performance Liquid Chromatography (HPLC) or Quantitative Nuclear Magnetic Resonance (qNMR) analysis. For several decades, the United States Pharmacopeia (USP) has set stringent requirements for balances used to weighanalytes for quantitative measures in its General Chapter 41, "Balances" [1]. These requirements are intended to ensure that any weighing error is small or even negligible compared to the error potential of other process steps within an analysis. Other pharmacopeias have recently established requirements for balances used for analytical purposes as well. These requirements are closely aligned with the approach stipulated by the USP. General Chapter 2.1.7 within the *European Pharmacopoeia* (Ph. Eur.) [2] and General Chapter 9.62 within the *Japanese Pharmacopoeia* (JP) [3] became official in 2022 and 2024, respectively, and since then, the *Indian Pharmacopoeia* (IPC) and the *Chinese Pharmacopoeia* (ChP) have published drafts of general chapters for balances to solicit industry feedback that align with the same direction [4, 5].

All weighing chapters in the pharmacopeias set specific requirements for the performance verification of balances that consist of periodic calibration and routine testing activities. The purpose of these requirements is to ensure that the instrument remains fit for its intended use by providing accurate weighing results based on specific metrological criteria. While the basic procedures and acceptance criteria for routine testing activities in all compendia are the same, Ph. Eur. has started setting requirements that are much more explicit concerning the application of underlying metrological concepts for calibration.

In Ph. Eur. General Chapter 2.1.7, calibration of weighing instruments has been associated with the estimation of measurement uncertainty for the first time in pharmaceutical regulations. Furthermore, the concept of as-found and as-left calibration is elaborated, which ensures traceability of measurement results

both before and after a service intervention when a balance is in routine operation. In addition, emphasis is placed on a risk-based approach for all weighing instrument performance verification activities as a basis for ensuring continuous fitness for intended use. This holistic metrological approach is also implemented in a new draft to revise USP General Chapter 41 [6] and in the draft of the balance chapter issued by IPC [4]. Therefore, the pharmacopeias are acting as strong ambassadors for implementing metrologically sound, risk-based strategies for the performance verification of weighing instruments globally.

Accurate weighing is also paramount for manufacturing to ensure that pharmaceutical products meet their predefined quality attributes. However, pharmaceutical regulations do not stipulate specific requirements for weighing in the production environment, instead leaving the definition of these requirements to the manufacturing organization. Still, the direction in which pharmaceutical QC regulations are developing might also serve as a solid example for updating metrological concepts for quality management of weighing within the production area. Specifically, the inclusion of measurement uncertainty in calibration activities and the consideration of as-found and as-left calibrations in production will help ensure traceability, and therefore the quality of measurement results.

UNDERSTANDING CALIBRATION

Regulatory Requirements for Calibration

Calibration is one of the key activities that must be performed periodically when instruments are used for quality-relevant measurements. Internationally, there are many standards that stipulate this requirement, e.g. ISO 9001, as well as pharmaceutical regulations such as Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP). As an example, US GMP [7] requires that: "Automatic, mechanical, or electronic equipment…shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance."

All major pharmacopeias require the use of a calibrated balance when weighing analytes for the purpose of quality control of pharmaceutical products, as stipulated in the respective general chapters for balances [1, 2, 3, 4, 5]. Personnel who work in quality control and quality assurance, either in the laboratory or in the production environment, are generally aware that calibration is mandated by regulatory and compendial guidance. However, outside of an actual calibration laboratory, there is still little true understanding of how calibration is defined or implemented. As noted, in the pharmaceutical industry, it is still widely believed that a balance is calibrated when a test load is placed on the weighing pan and the indication is compared with the reference value of the mass of the test weight.

The *European Pharmacopoeia* was the first compendium specially set out to overcome this misconception in the General Chapter 2.1.7, "Balances for Analytical Purposes," by spelling out the calibration requirement as follows: "Calibration is part of balance qualification and is performed by the user or by a suitable, competent body. Its aim is to establish traceability of measurement results to the [International System of Units] (metrological traceability). The calibration results include measurement uncertainty and are documented in a calibration certificate."

This explicit statement that defines calibration in terms of traceability and measurement uncertainty is replicated by the latest draft to revise USP General Chapter 41 [6]. It has also been implemented in JP General Chapter 9.62 and the drafts issued by IPC and ChP, which have adopted this approach and require a statement on measurement uncertainty when a balance is calibrated.

For many years, the USP has referred to measurement uncertainty in the glossary of USP General Chapter 1058, "Analytical Instrument Qualification" [8], which contains the same definition of calibration that is presented in the International Vocabulary of Metrology (VIM) [9]. However, all USP general chapters with numbers between 1000 and 1999 are for information only and cannot be legally enforced. Therefore, the requirement for inclusion of measurement uncertainty in calibration, as per the recent updates of the pharmacopeial chapters on balances, is a big step towards a metrologically sound interpretation of calibration.

The quality of calibration activities, when performed according to the principles outlined in the VIM, can be supported by accreditation under the ISO/IEC 17025 standard [10]. Accreditation by an accreditation body is the formal process that confirms a calibration laboratory's competence and compliance with requirements stipulated by ISO/IEC 17025. While accreditation is not a formal requirement of pharmaceutical regulations, calibration activities executed by an accredited calibration laboratory are becoming widely recognized as a supportive element in achieving compliance with applicable clauses of GLP and GMP regulations. As per ISO/IEC 17025, measurement uncertainty is an integral part of any calibration activity and therefore complements the latest pharmacopeial requirements.

Harmonizing Calibration Practices for Non-Automatic Weighing Instruments

Pharmaceutical regulations do not stipulate a specific method for the calibration of weighing instruments, so users typically refer either to internal procedures or to widely available and generally accepted reference documents. For balances and scales, which can also be described as non-automatic weighing instruments, many calibration guidelines exist at the national level, most of them based on the concepts described in the "Guide to the Expression of Uncertainty in Measurement (GUM) [11]." While these guidelines are generally quite similar, they differ in certain details, which has made it difficult, if not impossible, to develop and implement a single calibration guideline on a global level. Over the last decade, activities in the scientific community have addressed this issue by creating a harmonized approach for calibration of non-automatic weighing instruments based on EURAMET cg-18 "Calibration of Non-Automatic Weighing Instruments," which is the most widespread guideline globally [12, 13].

While EURAMET Calibration Guidelines No.18 (cg-18) are globally recognized, local calibration guidelines have subsequently been

developed based on its principles. In China, the national calibration specification JJF 1847 "Calibration Specification for Electronic Balances" was enacted in 2020 [14] to address the calibration of balances for the first time. JJF 1847 is fully aligned with the procedures and uncertainty estimation of EURAMET cg-18. In the United States, the recently updated document ASTM E898 "Standard Practice for Calibration of Non-Automatic Weighing Instruments" [15] is also fully commensurate with EURAMET cg-18 and supports the international harmonization of balance and scale calibration within the United States.

The approach of associating measurement uncertainty with calibration results in the general chapters on balances within the pharmacopeias fosters the global harmonization of calibrating weighing instruments using EURAMET cg-18 as the underlying guideline. Furthermore, in the draft to USP General Chapter 41, EURAMET cg-18 and ASTM E898 are specifically mentioned as calibration guidelines that fulfill pharmacopeial requirements for calibration.

As-Found and As-Left Calibration

In any discussion of calibration, it is essential to introduce the concept of adjustment as it relates to measuring instruments. Adjustment is defined in the International Vocabulary of Metrology (VIM) as a:

> "Set of operations carried out on a measuring system so that it provides prescribed indications corresponding to given values of a quantity to be measured."

In other words, adjusting an instrument involves modifying its indications so they correspond as closely as possible to the quantity values of the applied measurement standards. Unfortunately, many users apply the terms "calibration" and "adjustment" interchangeably or incorrectly. It is common for users to refer to calibrating a weighing instrument when they actually mean adjusting it. The VIM emphasizes this distinction, stating:"

> "Adjustment of a measuring system should not be confused with calibration, which is a prerequisite for adjustment. After an adjustment of a measuring system, the measuring system must usually be recalibrated."

This concept is reinforced in General Chapter 2.1.7 of the *European Pharmacopoeia*:

> "To ensure traceability, it is recommended to perform calibration before any maintenance operation is carried out that significantly alters its measurement performance. Significant operations include repairs, transfer of the balance to another location or mechanical adjustment of one or more weighing parameters. The balance must be re-calibrated after significant operations. Re-calibration is not necessary after less significant operations, which include levelling the balance or adjustment using built-in weights."

With this statement, the *European Pharmacopoeia* establishes a solid foundation for promoting the concept of as-found and as-left calibration as essential components of ensuring the traceability and validity of measurement results obtained from balances during routine use in the pharmaceutical industry.

- As-found calibration ensures traceability of all measurements performed prior to any adjustment on the instrument.
- As-left calibration ensures traceability of all measurements performed after the intervention.

The USP has adopted this approach in its recent draft update of General Chapter 41, and the IPC has implemented similar language in its draft balance chapter in their compendium. It is anticipated that other pharmacopeias will evaluate this approach with respect to calibration and eventually set similar requirements in their compendia with the objective of harmonizing pharmaceutical requirements for the metrology of weighing at an international level.

It is important to analyze the requirements of ISO/IEC 17025 with respect to as-found and as-left calibration. Paragraph 7.8.4.1 states that calibration certificates should include "the results before and after any adjustment or repair, if available."

This requirement is commensurate with the previously mentioned statement in the VIM and emphasizes the metrological importance of both calibration activities.

Calibration of scales in the production environment should follow the same principles, as measurement traceability during manufacturing is equally critical to traceability of measurements during analytical processes. Furthermore, in light of GMP requirements to ensure proper performance of electronic equipment, as-found calibration provides a basis for determining whether an instrument fulfilled metrological requirements prior to any performance modification (i.e., adjustment or repair see Figure 1).

Recently, the concept of Target Measurement Uncertainty (TMU) has come into frequent use as a fundamental metrological requirement for assessing whether an instrument is fit for its intended use [16, 17]. In other words, an instrument is considered fit for its intended use if its measurement uncertainty—derived during calibration—does not exceed a predefined threshold. This assessment enables users to determine whether an instrument needs to be adjusted.

If the measurement uncertainty estimated during the as-found calibration meets the TMU with a sufficiently high safety margin, an adjustment of the instrument may be unnecessary, rendering the subsequent as-left calibration obsolete. In such cases, the as-found calibration serves as the as-left calibration. It is worth noting that users often refer to "accurate measurement results" if they meet the TMU. However, TMU may not be the sole criterion for determining fitness for its intended use; additional requirements may need to be fulfilled.

For balances and scales, the measurement uncertainty derived from calibration results can be used to calculate the minimum weight— the smallest quantity of material that must be weighed to achieve a specified relative TMU. Minimum weight is therefore

a critical factor in determining whether a balance is capable of producing the required accuracy for a given application. There are more details on the concept of minimum weight in the literature [12, 13] .

ROUTINE TESTING

Defining Accuracy and Precision

Because calibrations are not carried out frequently—usually once or twice per year— it is considered best practice for users to conduct routine testing between calibration intervals. However, before analyzing routine testing as a critical part of weighing instrument performance verification in pharmaceutical regulations, it is essential to understand how accuracy and precision are defined within the pharmaceutical industry.

Specifically, the term "accuracy" has a different meaning within the pharmaceutical industry compared to its definition in VIM (see Figure 2). According to ICH Q2(R2) [18], "accuracy" is defined as:

> "The accuracy [...] expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value or set of values measured."

This concept is called "trueness" in all other fields of metrology and defined accordingly in the VIM. It characterizes the deviations of a series of measurements from a reference value.

> "Precision," by contrast, is defined similarly in both pharmaceutical and metrological contexts. ICH Q2(R2) states:
>
> "The precision [...] expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple samplings of the same homogeneous sample under the prescribed conditions [...]."

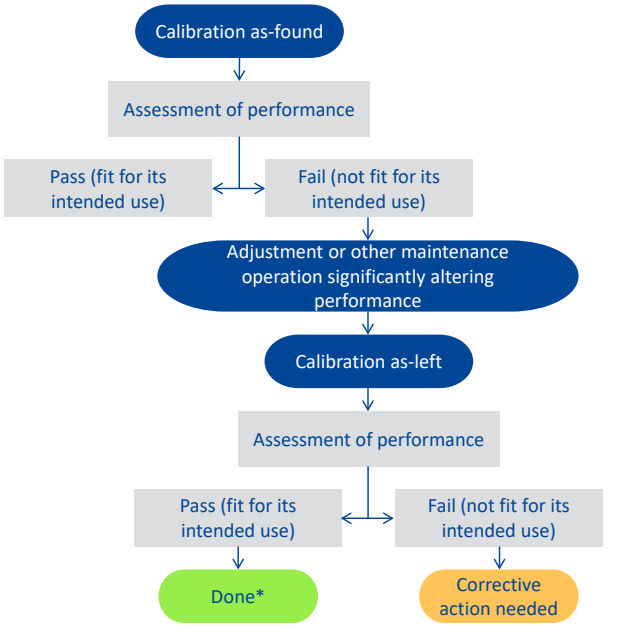
Precision characterizes how close together a series of measurements are under defined measurement conditions.

These definitions are important in the context of routine testing for balances to ensure they remain fit for their intended use. Pharmacopeias define specific tests for assessing accuracy and precision in their general chapters on balances. These tests stipulated by the pharmacopeias are designed to evaluate both systematic and random errors, which are limited when specific acceptance criteria, for tests that assess systematic and random errors, are defined.

Assessment of Accuracy and Precision

Routine testing activities aim to verify that weighing instruments fulfills predefined acceptance criteria during routine operation . Routine testing activities are specifically required by pharmaceutical regulations. While GMP regulations do not prescribe specific tests or acceptance criteria, pharmacopeias usually provide more detailed guidance.

Figure 1: Flow diagram of calibration and adjustment activities. The assessment of calibration results confirms whether the instrument is fit for its intended use. As-found calibration ensures the traceability of all preceding measurements that have been carried out on the instrument, while the as-left calibration ensures traceability of all subsequent measurements.



*As-left calibration can be omitted if as-found is successful.

Figure 2: Correlation between precision, trueness and accuracy based on their definitions in the VIM. Note that ICH uses the term "accuracy" instead of "trueness." Furthermore, ICH does not provide an equivalent for the VIM definition of "accuracy." In ICH terminology, the combination of accuracy and precision corresponds to what the VIM defines as accuracy.

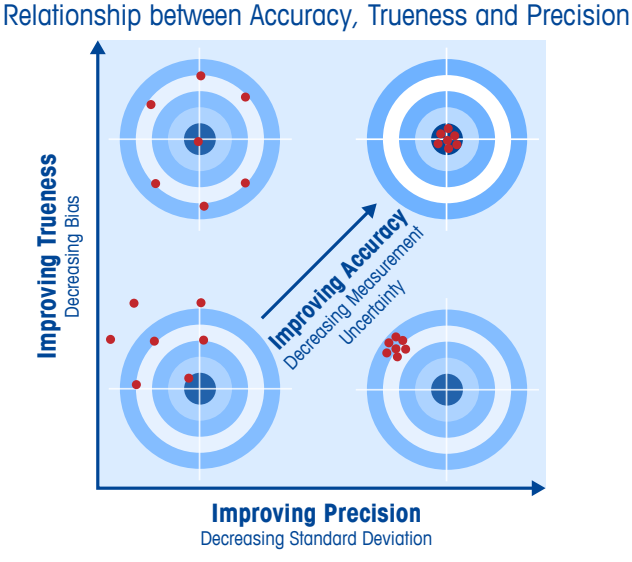
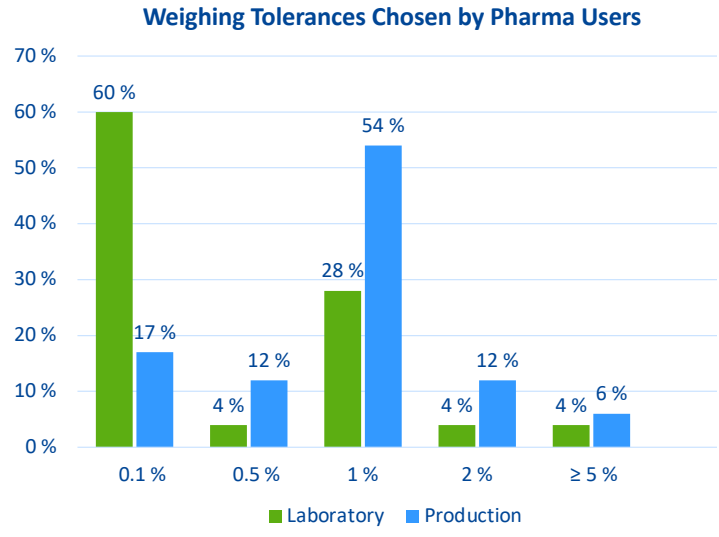


Figure 3: Typical values for tolerances or target measurement uncertainties (TMU) in laboratory and production applications within the pharmaceutical industry. For laboratory applications, most cases are governed by pharmacopeial requirements (0.10 % limit value for accuracy and precision). In manufacturing, tolerances are generally wider and depend on the criticality of individual weighing applications. This figure is based on a 2025 survey conducted by Mettler-Toledo, covering 56260 balances installed in laboratory environments and 12257 scales installed in production environments [19].



Laboratory: 56260 / Production: 12257/ Grand Total: 68517 //
Based on survey results from 2020 – 2025

Historically, the USP has defined two specific tests, and associated acceptance criteria, to assess the systematic and random error of balances. With a relative limit value of 0.10 %, the acceptance criteria for random and systematic errors defined in the pharmacopeias are quite stringent and ensure that the weighing step within analytical procedures is not the limiting factor in the overall accuracy of analytical procedures.

As previously noted, GMP regulations do not stipulate specific weighing requirements for pharmaceutical production. Therefore, it is the responsibility of individual organizations to define appropriate acceptance criteria for weighing instruments used outside the quality control laboratory. These criteria are typically expressed as a tolerance or a target measurement uncertainty (TMU), ranging from 0.1 % to 1 %, depending on the criticality of the weighing process and the potential impact of inaccurate measurements on production quality (see Figure 3) . However, some organizations may still struggle to define appropriate weighing requirements that are commensurate with the quality attributes of the Active Pharmaceutical Ingredient (API) or the finished pharmaceutical product, due to limited regulatory guidance.

Rounding Rules for Assessment

IIt is important to understand the rounding rules that are applied throughout all chapters of the pharmacopeias. Considering the Ph. Eur. description of the rounding rules in the General Notices section under "Limits" as representative for all pharmacopeias, the rule reads [20]:

> "In determining compliance with a numerical limit, the calculated result of a test or assay is first rounded to the number of significant figures stated [...]. The limits, regardless of whether the values are expressed as percentages or absolute values, are considered significant to the last digit shown (for example, 140 indicates 3 significant figures). The last figure of the result is increased by one when the part rejected is equal to or exceeds one half-unit, whereas it is not modified when the part rejected is less than a half-unit."

USP has implemented the same rounding rules, as described in the General Notices and Requirements section 7.20, which includes example illustrating how compendial requirements are applied [21]. In practice, mathematical rounding rules are applied to observed or calculated values based on the number of decimal places of the limit expression (the acceptance criterion). For example, a relative standard deviation of 0.1049 %, determined during a repeatability test to assess the precision of the instrument, would be rounded to 0.10 % (which corresponds to the number of decimal places of the 0.10 % acceptance criterion). With this value, the balance would pass the repeatability test. However, a relative standard deviation of 0.1050 % would be rounded to 0.11 %, resulting in a failed test. Note that this rounding procedure differs significantly from rounding rules in other fields of applied and legal metrology, where the formatting of any given limit value has no influence on the rounding of a measurement result.

Risk-Based Approach for Performance Verification

As previously noted, regulations often lack specificity regarding how instruments should be calibrated and tested, and they typically do not indicate specific time intervals for the tests—other than stipulating that calibrations and tests should be performed periodically. In metrology, guidance documents, such as the International Organization of Legal Metrology (OIML)/International Laboratory Accreditation Cooperation (ILAC) co-publication *Guidelines for the Determination of Recalibration Intervals of Measuring Equipment* [22] outline key factors to consider when determining calibration and testing intervals:

- A requirement for measurement uncertainty
- Risk exceeding predetermined limits or accuracy requirements in use
- Manufacturer's recommendations
- Expected extent and severity of equipment use
- Environmental conditions
- Frequency, quality, and results of intermediate checks

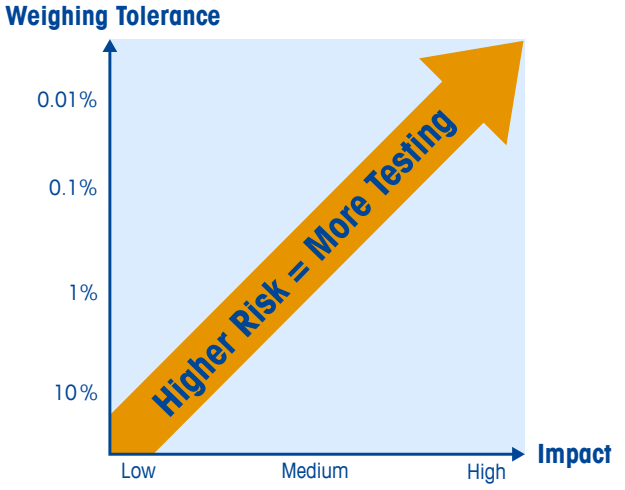
One important consideration in defining appropriate calibration and testing methods and intervals is the risk associated with the specific application. According to ICH Q9, risk is defined as "the combination of the probability of occurrence of harm and the severity of that harm [23]."

In weighing applications, it is assumed that the more stringent the accuracy requirements of a weighing process are, the higher the probability that the weighing result may not meet the requirements. In such cases, calibration and testing frequencies should be increased to mitigate risk. Similarly, when the potential impact of inaccurate weighing is severe—such as compromising product quality—more frequent calibrations and tests should be performed. By increasing the frequency of calibration and testing in high-risk scenarios, the probability of undetected measurement errors is reduced. This approach effectively offsets the elevated risk associated with critical weighing processes, thereby lowering the likelihood of occurrence of the impact, and hence, offsetting the increase of risk of inaccurate weighing processes that otherwise would occur.

Given the preceding discussion, , it is important to address a frequent misconception that is prevalent in the pharmaceutical industry when it comes to routine testing between calibration activities. Many quality control professionals refer to a "daily balance test," which typically assesses sensitivity—that is, the systematic error near balance's maximum capacity—without assessing its repeatability. Daily balance tests are anchored in the mindset of generations of operators who worked with mechanical balances, when daily checks were advisable due to wear, tear, and abrasion of critical mechanical components.

However, such daily balance checks are no longer required for electronic balances, and especially for electronic balances with built-in adjustment weights. This internal weight have rendered daily sensitivity testing with external reference weights largely obsolete. This shift is supported by guidance such as the United Kingdom Accreditation Service (UKAS) LAB 14 guidance document

Figure 4: Example of the implementation of a risk-based approach for the performance verification of weighing instruments. The higher the impact of inaccurate weighings—and the smaller the required weighing tolerance or target measurement uncertainty—the higher the risk that the instrument may not be fit for its intended use. This risk is mitigated by increasing appropriate performance verification activities.



"Calibration of Weighing Machines. [24]. The guide states:

> "Historically the best advice has been to perform daily checks, however, as is the case for calibration, the frequency of these checks should be determined on the basis of the risk associated with the weighing application."

Further support for this approach is found in Ph. Eur. General Chapter 2.1.7, which states:

> "In addition to testing weighing instruments with external weights, it is accepted practice to adjust the instruments by means of built-in weights. This makes it possible to reduce the frequency of sensitivity tests with external reference weights. For electronic balances with a built-in weight, daily sensitivity testing with an external reference weight is not considered necessary [...]."

This position is also reflected in guidance issued by the US FDA [25], which states:

> "For a scale with a built-in auto-calibrator, we recommend that external performance checks be performed on a periodic basis, but less frequently as compared to a scale without this feature. The frequency of performance checks depends on the frequency of use of the scale and the criticality and tolerance of the process or analytical step."

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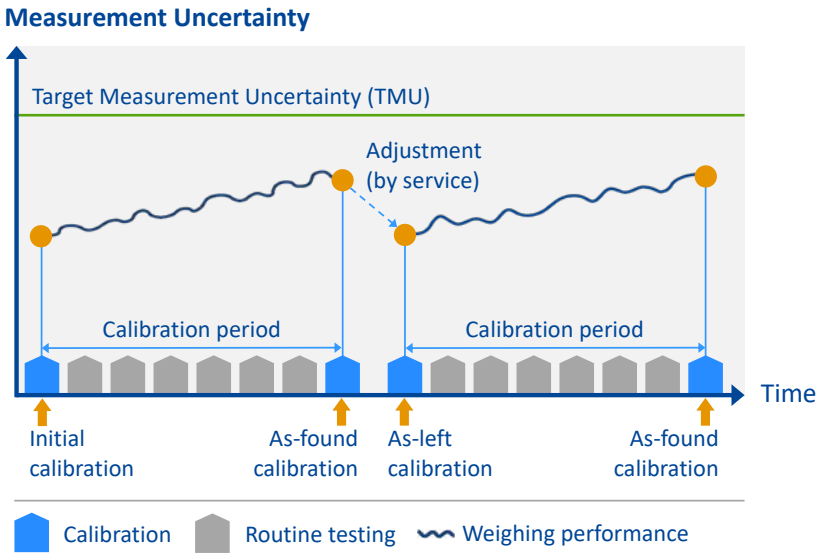
Figure 5: Holistic approach for the performance verification of weighing instruments. The as-found and as-left calibration is supplemented by appropriate routine testing activities to ensure that the instrument is continuously fit for its intended use, such as maintaining measurement uncertainty below the required target measurement uncertainty (TMU).



Instead of stipulating a daily balance check, pharmaceutical reference documents now focus on a risk-based approach for performance verification. This approach considers factors such as the OIML/ILAC categories (see Figure 4). For example, USP General Chapter 1251 "Weighing on an Analytical Balance" [26] states:

> "The frequency of the balance check depends on the risk of the application and the required weighing tolerance."

The literature provides more details on the lifecycle management of weighing instruments using a risk-based approach, highlighting its influence on accuracy, productivity, safety, and compliance [27, 28].

Relating As-Found and As-Left Calibration to Routine Testing

As previously noted, regulatory guidance requires an as-found calibration prior to a significant modification of the instrument (e.g., repair or adjustment with external test weights). Results of such a calibration are also used to assess whether an instrument is still fit for its intended use—specifically, whether all preceding measurements on the device fulfill the respective user requirements, such as a target measurement uncertainty TMU).

However, it would be detrimental to the weighing process to observe non-compliance based on an as-found calibration result, as it may impact the reliability of an undetermined number of preceding measurements—extending back to the last as-left calibration in the absence of routine testing. Therefore, periodic routine testing activities between calibrations are imperative to ensure that the instrument remains fit for its intended use. Routine testing can provide an early warning about a potential drift of the instrument that could lead to measurements that no longer fulfill user requirements.

Pharmacopeial standards support this approach by prescribing specific tests for assessing accuracy and precision, which serve this purpose exactly. Therefore, as-found and as-left calibrations and routine testing are all indispensable parts of a state-of-the-art approach for the quality management of weighing instruments. Combining them into this holistic practice ensures fitness for intended use across the lifetime of the instrument (see Figure 5). Ensuring these activities are well-understood in analytical and QC laboratories and extending them to production will help to assure the quality of weight-based measurements across the pharmaceutical value chain for easier compliance, better product quality, and heightened consumer safety.

DISCUSSION AND CONCLUSION

With respect to the lifecycle management of weighing instruments, the pharmaceutical industry has begun implementing concepts that are ever more anchored in metrology. While the outdated concept of a daily balance check remains prevalent in the minds of many users, a growing number of reference documents applicable to the pharmaceutical industry are embracing state-of-the-art methods for the testing and calibration of balances and scales based on risk assessment and management. Within a risk-based approach, the likelihood of inaccurate measurements and the potential impact of such errors would be assessed and offset by appropriate performance verification activities to reduce the risk to an acceptable level.

Recent interpretations of calibration within the pharmacopeias—aligned with the definition in the *International Vocabulary of Metrology* (VIM)—constitutes a quantum leap concerning the adoption of a more scientific interpretation of metrology within the pharmaceutical industry. Furthermore, the importance of as-found and as-left calibrations in ensuring the traceability of measurement results obtained by an instrument during routine use is being incorporated into pharmaceutical quality management systems.

In recent years, more pharmacopeias have expanded their regulatory frameworks with the objective of following the metrological approach initiated by Ph. Eur. in General Chapter 2.1.7, "Balances for Analytical Purposes." This trend is serving to foster a globally harmonized approach on metrology for balances used within the pharmaceutical industry.

These concepts should be applied in a similar way to weighing instruments across all pharmaceutical applications, as scales in the production area constitute a critical link in the pharmaceutical value chain. A holistic approach to the quality management of weighing instruments will help to ensure that balances and scales remain fit for their intended use, and that they are capable of promoting weighing accuracy, production quality, and consumer safety.

The consideration of measurement uncertainty for weighing processes may encourage its broader application across analytical and production workflows. By defining quality attributes for the final product and incorporating applicable quality control activities that consider measurement uncertainty, pharmaceutical companies could validate process outcomes on a more scientifically rigorous basis.

References

1. United States Pharmacopeia (USP). "General Chapter 41–Balances." USP–NF. Rockville, MD, US, : United States Pharmacopeial Convention; 2025.
2. European Pharmacopoeia (Ph. Eur.). "General Chapter 2.1.7–Balances for Analytical Purposes." Ph. Eur. Supplement 10.6 ff. Strasbourg, France: EDQM Council of Europe; 2025.
3. Japanese Pharmacopoeia (JP). "General Chapter 9.62–Measuring Instruments, Appliances–Balances and Weights." JP 18th Edition, 2nd Supplement. Tokyo, Japan: Ministry of Health, Labour and Welfare; 2024.
4. Indian Pharmacopoeia Commission. "Draft Proposal for Comments and Inclusion in the Indian Pharmacopoeia, General Chapter 2.1.7–Balance used in Analytical Procedure, Version 2." Ghaziabad, India: IPC, 2024..
5. Chinese Pharmacopoeia (ChP). "Draft Guideline 9032–Weighing Guideline on Electronic Balances for Analytical Purposes." Beijing, China: ChP; 2025.
6. United States Pharmacopeia (USP). "Draft, General Chapter 41–Balances." Pharmacopeial Forum. PF50(5). 2024. Rockville, MD, US. United States Pharmacopeial Convention..
7. U.S. Code of Federal Regulations. Title 21, Part 211, Section 211.68 (a). "Current Good Manufacturing Practice for Finished Pharmaceuticals (Automatic, mechanical, and electronic equipment)." Washington, D.C.: Government Publishing Office, 2025.
8. United States Pharmacopeia. "General Chapter 1058–Analytical Instrument Qualification." USP NF. Rockville, MD, US, United States Pharmacopeial Convention; 2025.
9. Joint Committee for Guides in Metrology (JCGM). International Vocabulary of Metrology–Basic and General Concepts and Associated Terms (VIM). JCGM 200:2012, 3rd ed. Sèvres, France: Bureau International des Poids et Mesures (BIPM), JCGM 200:2012.
10. International Organization for Standardization (ISO) and International Electrotechnical Commission (IEC). "General Requirements for the Competence of Calibration and Testing Laboratories." ISO/IEC 17025:2017. Geneva, Switzerland: ISO/IEC, 2017.
11. Joint Committee for Guides in Metrology (JCGM). "Evaluation of Measurement Data—Guide to the Expression of Uncertainty in Measurement (GUM)." Bureau International des Poids et Mesures (BIPM) 100:2008,. Sèvres, France, 2008.
12. EURAMET cg-18, "Guidelines on the Calibration of Non-automatic Weighing Instruments", 4th edition. EURAMET; 2015. EURAMET cg-18. Braunschweig, Germany.
13. Fritsch, K. "EURAMET cg-18–State-of-the-Art Calibration Guideline for Non-Automatic Weighing Instruments." Acta IMEKO Vol. 8, No. 3 (2019): Article 3.
14. State Administration for Market Regulation (SAMR) of the People's Republic of China. "Calibration Specification for Electronic Balances." JJF 1847-2020. Beijing, China: SAMR, 2020. JJF 1847-2020.
15. ASTM International. "Standard Practice for Calibration of Non–automatic Weighing Instruments." ASTM E898-20. Conshohocken, PA: ASTM International, 2020. ASTM E898-20.
16. United States Pharmacopeia (USP). "Draft, General Chapter 1058–Analytical Instrument Qualification." USP Pharmacopeial Forum PF51(2), 2025. Rockville, MD, US. United States Pharmacopeial Convention.
17. Weitzel, J et. al., "Stimuli to the Revision Process–Measurement Uncertainty Evaluation Relevant to Analytical Instrument and System (AIS) Qualification–The Role of Measurement Uncertainty Concepts within the AIS." USP Pharmacopeial Forum PF48(2). Rockville, USA, 2022. United States Pharmacopeial Convention.
18. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "Validation of Analytical Procedures." ICH Q2(R2). Geneva, Switzerland: ICH, 2023.
19. Mettler-Toledo. Survey of the Pharmaceutical Industry. Data collected between 2020 and 2025 (previously unpublished).
20. European Pharmacopoeia (Ph. Eur.) "General Notices." Ph. Eur. 11th Edition, EDQM Council of Europe, Strasbourg, France, 2025
21. United States Pharmacopeia (USP). "General Notices and Requirements." USP–NF, Rockville, MD, US. United States Pharmacopeial Convention; 2025.
22. International Laboratory Accreditation Cooperation (ILAC) and International Organization of Legal Metrology (OIML). "Guidelines for the Determination of Recalibration Intervals of Measuring Equipment." ILAC-G24/OIML D 10:2022. Silverwater, Australia, and Sèvres, France, 2022.
23. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). "Quality Risk Management." ICH Q9(R1). Geneva, Switzerland: ICH, 2023.
24. United Kingdom Accreditation Service (UKAS) LAB 14, Edition 7. "Guidance on the calibration of weighing machines used in testing and calibration laboratories." United Kingdom Accreditation Service. Chertsey, UK: UKAS; 2022.
25. US Food and Drug Administration (FDA). "FDA Questions and Answers on Current Good Manufacturing Practice Requirements/Laboratory Controls." https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practice-requirements-laboratory-controls. Accessed June 6, 2025.
26. United States Pharmacopeia (USP). "General Chapter 1251–Weighing on an Analytical Balance." USP–NF. Rockville, MD, US, 2025. United States Pharmacopeial Convention; 2025.
27. Reichmuth, A, Fritsch, K. "Good Weighing Practices for the Pharmaceutical Industry–Risk-Based Qualification and Life Cycle Management of Weighing Systems." Pharmaceutical Engineering. Vol. 29 No. 6, 2009. ISPE. North Bethesda, MD, US.
28. Fritsch, K. "GWP®–The Science-Based Global Standard for Efficient Lifecycle Management of Weighing Instruments." J. Meas. Sci., Vol. 8 No. 3, 2013. NCSLI. Glen Ellyn, IL, US. NCSLI.

NOTE: At the time of printing, the draft to change USP General Chapter 41 (referenced in [6]) was approved, and will be integrated in USP-NF 2026, Issue 1, replacing the existing General Chapter 41 (referenced in [1]). USP-NF 2026, Issue 1 will become official 1 February 2026. With the same timeline, a draft to change USP General Chapter 1251 (not referenced) was approved and will be integrated in the same edition of USP-NF, replacing the existing General Chapter 1251 (referenced in [26])."

About the author

Klaus Fritsch, PhD, is Compliance Manager in the Laboratory Weighing Global Business Area within Mettler-Toledo. He has worked with Mettler-Toledo since 2005, serving as a Senior Metrologist and industry consultant to support compliance with applicable regulations in the use of weighing instruments. Fritsch is also a member of the USP expert panel responsible for the General Chapters <41> and <1251> on balances, the Ph. Eur. expert panel responsible for the General Chapter 2.1.7 on balances for analytical purposes; the EURAMET working group responsible for the calibration guideline cg-18 on non-automatic weighing instruments; and the ASTM International working group responsible for the calibration guideline ASTM E898 on non-automatic weighing instruments. Fritsch received his PhD in physics from the Technical University of Munich, Germany. He joined ISPE in 2005.

ENSURING DRUG PRODUCT SAFETY

Compliance Strategies Under USP 665 and 1665

By Giovanna Cantoni PhD

The United States Pharmacopeia (USP) Packaging and Distribution Expert Committee approved chapters 665 and 1665 in 2024. These chapters establish clear and general guidelines for the use of plastic materials in process equipment used within the pharmaceutical and biotechnology industries. Their publication has raised new questions regarding the role of polymeric materials in manufacturing systems and their potential impact on the quality of the final drug product. The new rules will be effective 1 May 2026, allowing time for industry-wide implementation.

This paper aims to open a discussion on the implications of these new rules and the challenges associated with evaluating the impact of plastic materials that may come into direct contact with the product or influence product quality of the drug product during processing. The analysis considers the entire equipment train involved in manufacturing. Packaging materials are not included in this discussion, as they are already addressed by dedicated ISO standards.

INTRODUCTION

Almost all process equipment used in the pharmaceutical industry contains some polymeric material that may come into direct contact with the drug product or any intermediate product. Furthermore, single-use systems (SUS) are becoming increasingly integrated into manufacturing processes in the biotech industry.

Guidance documents USP 665, "Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products," and USP 1665, "Characterization and Qualification of Plastic Components and Systems used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products," have been issued to address a previously unmet need for standardized methods to evaluate the impact of polymeric materials on the quality of drug products. These chapters provide new guidance with a focus on risk-based assessments.

BACKGROUND

Typical manufacturing workflows consist of multiple production steps necessary to convert raw materials into a pharmaceutical or biopharmaceutical drug substance (DS) or a drug product (DP). Manufacturing processes may expose the final product and its intermediates in possible direct contact with plastic materials, as the equipment may be partially or entirely constructed from polymers. In fact, polymeric materials are widely used in SUSs and piping, and they may contain additives such as antioxidants, stabilizers, lubricants, plasticizers, colorants, and any other component which, when coming in contact with the different materials used in different steps of a manufacturing process, these additives may be released during processing and potentially be present in the final DP impacting its quality and efficacy.

The DP may contain the cumulative sum of the molecules leached from all materials present in the process equipment used throughout manufacturing, unless mitigated by downstream steps such as purification or filtration.

This USP chapter focuses on Process Equipment-Related Leachables (PERLs), defined molecules with the potential to alter critical quality attributes (CQA) and impact the safety, quality, identity, potency and/or purity (SQuIPP) of the DP or DS.

Production intermediates, DS, or DP may come into contact with plastic components present in different manufacturing systems during the manufacturing process. For this reason, USP 1665 contains guidelines for characterizing plastic components used in manufacturing drug products in order to ensure that plastic materials and components do not adversely affect drug product quality or patient safety.

The aim of USP 665 is to evaluate throughout the entire production process—from raw materials to DS and ultimately to DP, any possible PERLs from plastic materials used somewhere along the process. Historically, manufacturers of single-use (SU) components conducted extractables studies and shared results with end users. However, the lack of standardized methods, solvents, and exposure durations made the component selection process challenging for users.

This chapter applies to all DPs, including pharmaceuticals (i.e. traditional small molecules product) and biopharmaceuticals (biologics, defined as products derived through biological processes such as antibody-drug conjugate (ADCs) or recombinant proteins). For biopharmaceuticals, the evaluation is intended to apply to both DS and DP.

Active pharmaceutical ingredients (API) produced via chemical processes, as well as precursors of non-biologic and non-biopharmaceutical DPs, are outside of the scope of this USP chapter.

The types of plastic material included in the evaluation of PERLs are both single-use systems (SUS), meaning manufacturing components designed for one-time use and disposal (such as bioreactors, media bags, tubing, samplers), and multiple-use systems (MUS), such as O-rings, gaskets, and filters. MUS components are intended for reuse following validated cleaning and sterilization procedures.

This chapter should be applied solely to process steps involving liquid or semisolid states, due the inherent tendency of plastic materials to have a greater interaction with materials in liquid or semisolid states compared to solids or gases.

Typical plastic materials that may be present in a pharmaceutical and biopharmaceutical processes are presented in Table 1 of the chapter, where they are divided into materials having different interaction timing:

- Short-time contact, simulated by a worst-case extraction time of –24 hours ± 1 hour
- Medium-time contact, requiring –168 hours (7 days) ± 4 hours

Long-time contact, requiring 504 hours (21 days) ± 8 hours. Among examples of components listed in the table for short-duration contact include chromatographic column housing, non-storage containers such as mixing bags, bioreactors, filters, filtration cassettes and other items commonly found in modern manufacturing facilities.

USP 1665 offers a detailed rationale for the scope and use of this chapter and provides additional information and guidance regarding the application and applicability of USP 665.

Among the materials considered to have short interaction times include small components such as O-rings, gaskets, and diaphragms. The evaluation of these components, however, is excluded in this chapter if they are constructed from rubber–based elastomers. In such cases, their evaluation, in terms of test method and specification, should follow the guidance provided in USP 381, "Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems."

Additional exclusions apply to plastic auxiliary items such as scoops, funnels, pipettes, and other components whose limited contact with the product, or whose material state, poses minimal risk of contributing PERLs to the process stream. Therefore, these items are not covered by this chapter.

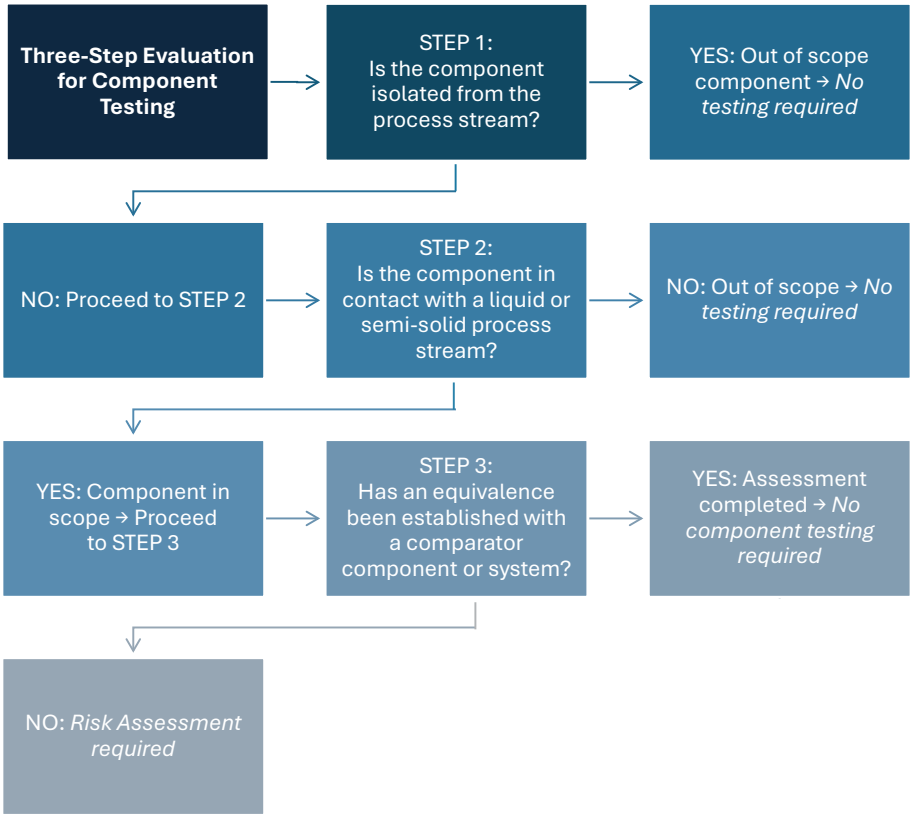
USP 1665 offers a detailed rationale for the scope and use of this chapter and provides additional information and guidance regarding the application and applicability of USP 665.

The testing described herein applies to components and systems that have not yet been qualified, as well as to previously qualified components whose usage conditions have changed.

Both USP c chapters clearly indicate the principle that the component user bears the responsibility to establish and justify how this c chapter should be applied to specific actions and to justify its relevance to the particular process stream used in pharmaceutical and/or biopharmaceutical manufacturing processes.

It is important to emphasize that USP General chapter 1665 is informational and does not constitute a statement of requirements. In contrast, USP 665 will become official on 1 May 2026, and will define requirements for products manufactured or marketed in the United States.

Figure 1: This decision-making flowchart outlines a structured three-step process to determine whether a component used in pharmaceutical or biopharmaceutical manufacturing requires testing. The evaluation considers the component's isolation from the process stream, its contact with liquid or semi-solid materials, and its equivalence to previously qualified components. Components deemed in scope and lacking established equivalence must undergo a risk assessment to evaluate potential impacts on drug product quality and patient safety.



USP 665 qualification process

Qualification testing of a component or system is necessary to demonstrate its suitability to produce an acceptable DS or DP. When appropriate, system qualification may be augmented by DS or DP testing to directly assess the impact of the manufacturing system on the product's key quality attributes.

The qualification process foresees a two-step approach:

1. Initial assessment of the plastic material
2. Risk assessment to determine the potential impact of PERLs that could adversely affect the quality of the DP, and to define the appropriate level of testing and evaluation for intermediates, DS, and DP.

The most effective way to ensure that a system is suitable for its intended use is to have well-characterized components constructed from rationally selected materials. This can be obtained by material and component characterization, which supports and justifies the selection process.

Qualification of plastic manufacturing components and systems involves:

- Component or system characterization by chemical testing (i.e., extractables profiling)
- Interpretation of test results to assess suitability for use, including toxicology evaluation

The initial assessment determines whether component testing is necessary. If so, a subsequent risk assessment should be conducted to define the appropriate level of testing based on the potential impact of PERLs on the quality of intermediates, DS, or DP.

Initial Assessment of Manufacturing System

This assessment evaluates the system's suitability for its intended

Figure 2: Testing requirements based on the results of component risk assessment.

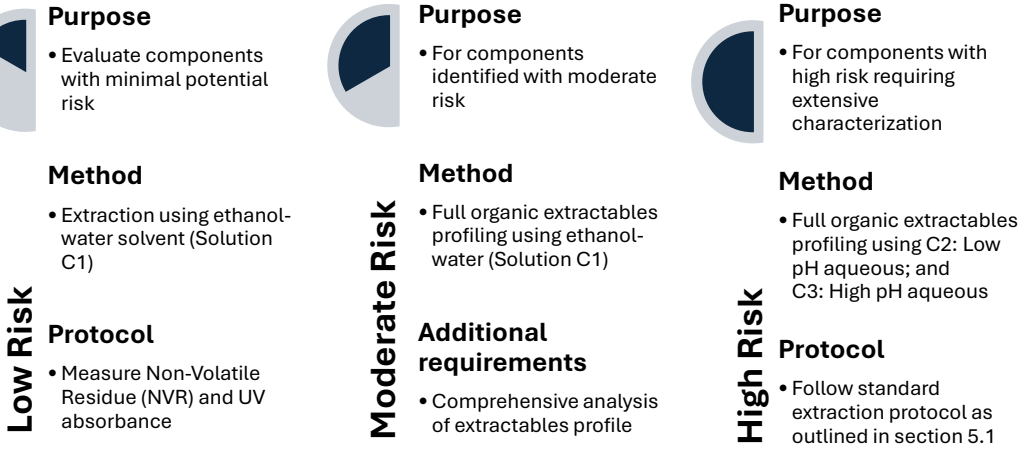
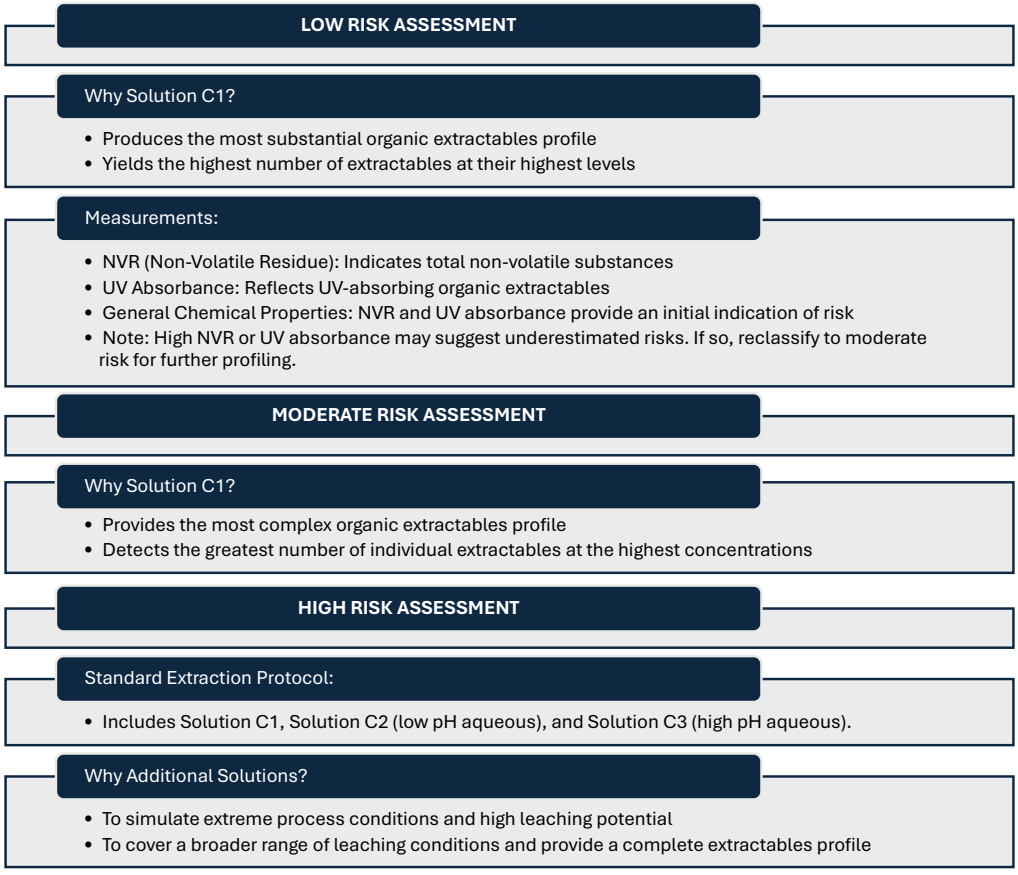


Figure 3: Testing solution selection based on the results of the risk assessment.



use without chemical characterization. The approach is schematically represented in the following flowchart.

The final step of the assessment addresses the equivalence of a manufacturing system with a previously qualified component or system.

Such equivalence is established based on the following criteria:

- Materials of construction have the same composition and are manufactured using similar processes
- Vendor preparation for use is performed in the same manner
- Design equivalence is maintained
- Functional equivalence in the performance is demonstrated
- User preparation for use is conducted in the same manner
- Conditions of use within the manufacturing process are equivalent
- An equivalent DS or DP with same composition and clinical application is used in manufacturing

While it is ideal for all seven criteria of equivalence to be fulfilled, essential equivalence may still be established based on the strong similarities between the component under evaluation and comparator. In this last case, the minor differences should be addressed through a risk-assessment approach.

The responsibility establishing and justifying equivalence to a comparator lies in the hands of the component user.

If no suitable comparator is present, or if equivalence cannot be demonstrated, the component must be characterized using a risk-based approach.

Risk Assessment

Component testing is conducted to evaluate the suitability of the component for its intended use. This assessment is based on the chemical and/or biological effects attributed to PERLs. The greater the risk of component unsuitability, the more extensive the degree of required testing will be.

Risk assessment is conducted using a risk evaluation matrix, which defines the dimensions of risk and enables quantification of individual risk factors. This approach facilitates the calculation of total risk and links the outcome to the appropriate level of characterization testing.

The risk assessment must consider a range of factors that influence the likelihood of leaching and the persistence of leachables. A robust evaluation of PERLs should address, at minimum, the following considerations:

- The chemical and physical nature of the contacted component, to establish its propensity for leaching
- The chemical nature of the process stream, to assess its potential to extract leachables
- The capability of downstream processing steps to eliminate, remove, or clear PERLs from the process stream, or to dilute the PERL to assess the unlikelihood of an adverse effect
- Inherent risk associated with the manufactured DP, considering route of administration, clinical dosage, and duration of standard clinical therapy

The outcome of the risk assessment is categorized as low, moderate, or high risk, and the extent of testing required for the component is determined accordingly. This correlation between risk level and testing requirements it outlined in Table 2 of USP 665 and schematically represented in Figure 2.

Standard Procedure and Extraction Solutions

USP 665 clearly defines conditions, solutions, and procedures to be followed for measuring potential leachables originating plastic components used in DS and/or DP manufacturing systems.

Standard Solutions

The three standard extraction solutions specified in chapter USP 665 are designed to simulate worst-case scenarios across a range of manufacturing conditions. These solutions are used for organic, acidic, and basic extraction studies during the evaluation of PERLs in plastic manufacturing components:

- Solution C1: Organic Extraction

A 50% ethanol/purified water solution used to simulate exposure to organic solvents, solubilizers, lipids, proteins, blood-derived components, and a broad range of organic and biological substances.

- Solution C2: Acidic Extraction
- A pH 3 salt solution) used to simulate low pH conditions, applicable to acidic process streams.
- Solution C3: Basic Extraction

A pH 10 buffer solution used to simulate high pH (alkaline) conditions. This solution is not interchangeable with more caustic solutions such as 0.5 N sodium hydroxide. Chapter 4.2.1 of USP 665 provides detailed instructions for the preparation of the above-mentioned standard solutions, or possible acceptable alternatives to be used in leachable studies.

For more effective testing of plastic components, pre-conditioning or processing is necessary in accordance with the manufacturer's instructions and intended use. This may include, for example, irradiation or steam sterilization.

Extraction Process

The standard extraction process should be dynamic, simulating real manufacturing conditions.

The extraction process outlined in USP 665 is designed to establish a standard extraction protocol that balances completeness and practicality, in order to ensure that the extracts provide meaningful data for component qualification in manufacturing systems.

These protocols should be applied in components and systems used in diverse manufacturing environments and in many different and varying conditions, depending on the product and process in scope.

If the test conditions have open access, and therefore a loss in the standard solution is possible, a necessary remedy should be found in order to maintain and control the possible loss in extraction volume.

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Extraction blanks—ions of the extraction solution not in contact with the test article—should be generated and tested to identify any chemical extracts from analytical artifacts.

When designing the extraction testing, it is essential to ensure that sufficient extract volume is available to support all required testing.

Some specific cases are provided describing procedures to be applied in different cases, such as extraction of aseptic connectors or disconnectors, bags, and other specific components.

In Section 4.2.2 of USP chapter 665 all details regarding the extraction process and specific case applications are reported and described.

Extract Testing

Extract testing is broadly divided into two categories depending on the aim of testing: chemical and biological testing.

Chemical testing can be supported in the following approaches:

- Extractables testing: identifies potential chemical substances that may leach from plastic components into the drug product under exaggerated conditions.
- Leachable testing: Detects and quantifies chemical substances that actually migrate into the drug product under normal storage and use conditions.

Biological testing, on the other hand, evaluates the potential health impact of leachables on the health of patients. They can be grouped as follows:

- Cytotoxicity testing: Conducted to determine if leachables from plastic components are toxic to cells or inhibit cell growth.
- Hemocompatibility testing: Performed to assess the interaction of leachables with blood products.

The most commonly employed chemical tests include:

- Non-Volatile Residue (NVR) testing: Utilizes extraction solution C1 associated with extraction blanks. Acceptance criteria for NVR result should comply with USP chapter 1665 .
- Ultraviolet (UV) absorbance: Also uses extraction solution C1 associated and extraction blanks. The differential UV absorbance must meet the acceptance criteria outlined in USP chapter 1665.
- Organic extractable profiling: Recommended when a moderate risk assessment outcome is identified. In such cases, both extracts and extraction blanks should be analytically tested.

For organic extractables, orthogonal chromatographic methods should be employed to estimate their presence and concentration. Extractables must be reported in accordance with USP chapter 1663 , considering the limits of detection (LoD) and quantitation (LoQ). Acceptance criteria should be defined based on safety and/or product quality risks, supported by toxicological assessments of individual extractables.

Alternative Extraction Approaches

USP chapter 665 provides flexibility for the qualification of plastic components used in pharmaceutical manufacturing. Alternative qualification procedures can be employed based on a thorough risk assessment and by providing a proper justification.

This flexibility allows for the adaptation of qualification procedures according to the specific risk profile of the component. It includes the use of existing data from previous qualifications or from similar components to support the qualification process, and requalification processes for components that undergo significant changes.

The following studies are permitted and recommended:

- Comparative studies: To demonstrate equivalence between a new or modified component and an already qualified comparator component.
- In silico models: To predict the behavior and interaction of leachables with the drug product using computational models.
- Bridging studies: To bridge data from existing studies to the new component, minimizing the need for extensive new testing.

It must be stressed that all the studies must be executed, reported, and archived by complying with Good Manufacturing Practice (GMP) requirements to ensure that alternative qualification procedures meet regulatory requirements and guidelines.

USP chapter 1665: Technical Guidance and Standard Procedures

USP 1665 provides foundational concepts and detailed guidance on the applicability and implementation of chapter <665>. It outlines qualification procedures for manufacturing components and systems within its scope.

The chapter aims to detail and document the technical procedures required to ensure that plastic components used in manufacturing systems do not release PERLs at concentrations that could pose risks to patient safety.

For non-metallic or non-glass materials, two other USP chapters should be considered: 338, concerning elastomeric materials, and 661.1, concerning a more general part related to plastic materials.

This chapter provides a detailed description of the procedures and considerations involved in the evaluation and initial assessment of plastic components used in pharmaceutical manufacturing. It offers guidance on the characteristics of extraction protocols and the type of studies to be performed, depending on the manufacturing system, process, and product in scope. It also gives guidance on analytical method techniques and acceptance criteria limits.

As an example, with respect to the extraction protocol, some limits are clearly stated:

- A maximum temperature of 40°C, which is considered the optimum in order to accelerate the extraction process without significantly altering the nature of the component.
- The duration, which is stated from a minimum of 1 day up to a maximum of 21 days to reflect both short-term and long-term contact conditions.

The level of details given should then be adapted to the specific case and used as a guideline in performing the assessment and the studies needed.

CONCLUSION

The requests and activities described in this article pose an important effort in all DP and/or DS manufacturing facilities, particularly considering that many new manufacturing facilities have been designed primarily around single-use systems (SUS).

USP chapter 665,which becomes a requirement on 1 May 2026, relies on the direction outlined in USP chapter 1665. Both chapters stress that the ultimate responsibility for assessing the potential impact of leachables from plastic materials present in manufacturing systems on the final product, is the responsibility of the final user (meaning the DP and/or DS manufacturer).

To meet these requirements , it will be necessary to first map the process, particularly the manufacturing systems in place and their association with specific process steps for the DP and/or DS in scope. Subsequently, an analysis of plastic components used manufacturing systems should be conducted based on available information from the provider or for use in other context. Consideration should also be given to the presence of identical systems operating under different conditions or in various parts of the facility, as this may influence the scope and prioritization of testing.

Once the test and parts are defined through a risk-based scientifically sound assessment, the parts involved should be considered as possible comparators for other manufacturing systems in the facilities, in case the process and product characteristics can be considered comparable.

Throughout this process, the primary importance should be the safety of the patient. The central challenge lies in understanding the types and concentrations of PERLs that may be present in the final product, and in correctly assessing the real toxicological impact on the patient.

References

1. USP <665>. "Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products." United States Pharmacopeia and National Formulary (USP–NF). Rockville, MD, US. United States Pharmacopeial Convention. 1 May 2026. https://doi.usp.org/USPNF/USPNF_M11135_02_01.html
2. USP <1665>. "Characterization and Qualification of Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products." United States Pharmacopeia and National Formulary (USP–NF). Rockville, MD, US. United States Pharmacopeial Convention. 1 May 2026. https://doi.usp.org/USPNF/USPNF_M11136_02_01.html

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12. Zhang J, Raghavachari R, Kirkpatrick D, Keire D, Xua X, Faustino P. "Analytical procedure development and proposed established conditions: A case study of a mass spectrometry-based NDSRI analytical procedure." *Journal of Pharmaceutical Sciences*. 2024;113(10). https://doi.org/10.1016/j.xphs.2024.07.022
13. Simeoni P, Deissler M, Bienert R, et al. "Using enhanced development tools offered by analytical Quality by Design to support switching of a quality control method." *Biotechnology and Bioengineering*. 2023;120(11). https://doi.org/10.1002/bit.28517
14. Gellermann G, Kirsch S, den Engelsman J. "Fine-tuning analytical development strategies for every phase." *Bioprocess Online*. Published 22 March 2024. https://www.bioprocessonline.com/doc/fine-tuning-analytical-development-strategies-for-every-phase-0001

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Expand Your Knowledge and Network at ISPE Annual Meeting & Expo

By Ciby Abraham, PhD



As professionals in pharmaceutical engineering, we are challenged to develop medications and therapies more quickly and less expensively than ever before while maintaining safety and efficacy. It can be hard to know where to turn when you have an issue you cannot resolve or difficult to find your next bit of inspiration. The ISPE Annual Meeting & Expo is a great opportunity for us to come together to network, learn, and have fun.

This year's ISPE Annual Meeting & Expo will be held 26 – 29 October in Charlotte, NC, US, and virtually. In addition to the 60 plus hours of educational information, the Exhibit Hall will be home to more than 200 exhibitors presenting the latest technologies and advancements in the industry, and there will be ample opportunity to network and connect at events like the FOYA Banquet and Awards Celebration, Welcome Reception, and Tuesday Night Celebration.

The conference features more than 160 speakers with educational tracks focused on many of the most important issues facing our industry. Here are just a few highlights on the agenda.

BIOLOGICS MANUFACTURING

The need for biologic therapies is rapidly increasing due to their effectiveness in treating complex diseases, including cancer, autoimmune disorders, and rare conditions. Advancing biologics manufacturing is vital to produce safe, effective, and affordable therapies at scale—directly impacting patient health, business viability, and the ability to respond to evolving healthcare needs. On Monday 27 October, Wei Huang, COO, Henlius Biopharmaceutical Ltd. will present, "Novel Technology Applied in Biologics Manufacturing," where she will discuss the technologies and strategies shaping the future of biologics manufacturing—a future defined by greater efficiency, quality, and accessibility through digital transformation. In her presentation she will give an update on the latest advances in continuous bioprocessing, real-time analytics, and AI integration—technologies which are at the forefront of modern biologics manufacturing.

ARTIFICIAL INTELLIGENCE AND REGULATORY COMPLIANCE

The use of artificial intelligence (AI) and machine learning (ML) is changing our industry and shaping the future of regulatory compliance. Managing AI in regulated life sciences is crucial because it protects patients, product quality, and data integrity, ensures compliance, builds trust, enables innovation, and promotes industry-wide consistency. The industry, regulators, and the public must trust that AI can be used safely and transparently. Without clear guidance, adoption may be slow, uneven, or risk-averse, holding back innovation.

On Monday 27 October, Afrah Mujeeb, Regulatory and Quality Co-Op, Access Vascular Inc., will present timely, practical guidance on leveraging AI/ML for regulatory excellence, addressing ongoing challenges, and preparing industry professionals for emerging global standards and ethical considerations in AI adoption. In her presentation, "AI/ML in Regulatory Decision: Compliance & Innovations," she will cover international perspectives and harmonization initiatives, and how, for example, major regulatory agencies like the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) are actively developing frameworks and guidance for AI/ML. The presentation will provide knowledge, tools, and strategies to safely, ethically, and effectively leverage AI/ML in regulatory contexts—helping companies gain a competitive edge, boosting compliance, and supporting better public health outcomes.

On Tuesday 28 October, Brandi Stockton, Founder, Managing Partner, The Triality Group, LLC, and Eric Staib, Vice President, Corporate Quality, Syneos Health will deliver a roadmap for leveraging AI in regulated GxP environments—promoting both innovation and compliance. Their presentation, "New GAMP® AI Guide Overview and Key Concepts," will equip industry professionals with the knowledge, structure, and confidence to safely and effectively integrate AI into regulated processes, fostering innovation while safeguarding compliance and patient safety. It addresses a pressing need for clear, harmonized guidance on AI in regulated environments, where industry best practices are still emerging and regulations are evolving.

SUCCESSFUL SUSTAINABILITY

Addressing the environmental footprint in pharmaceutical manufacturing is vital for protecting the planet, maintaining business viability, meeting stakeholder expectations, and shaping a more sustainable future for the industry and society. Pharmaceutical

manufacturing consumes significant energy and resources, contributing to carbon emissions, water use, and waste production. Reducing environmental impact is essential to protect ecosystems and address the urgent challenge of climate change.

Sustainability should be at the forefront of decisions as we build new facilities or renovate existing ones. On Monday 27 October, Melanee Short, Head of Sustainability, Global Engineering, Sanofi, will demonstrate how innovative partnerships and gamification can create lasting change, drive measurable sustainability outcomes, and inspire other organizations to adopt similar approaches. Her presentation, "Leveraging Competition to Drive Sustainability," will equip industry professionals with new ideas and potential methods to advance environmental sustainability, boost operational performance, and foster a culture of continuous improvement, helping the entire sector move toward a more sustainable future.

HOW DIGITAL INNOVATIONS CAN ADVANCE ATMPS

Advanced Therapy Medicinal Products (ATMPs) have the potential to change lives and cure diseases that we previously thought were incurable, but the cost to develop and manufacture these therapies can be cost prohibitive. Scaling up autologous and allogeneic cell therapies is challenging due to variable processes, manual operations, and unpredictable patient-specific demands. Overcoming manufacturing bottlenecks in cell therapy is crucial because it directly impacts patient health, industry advancement, product quality, operational cost, and readiness for the future. On Tuesday 28 October, George Todorov, Senior Process Specialist, IPS, and Stephen Lane, Industrial Analyst II, Modeling & Simulation, IPS, will present, "Simulation-Driven Solutions for Cell Therapy Manufacturing Ramp-Up." Their approach is noteworthy because it goes beyond theoretical discussion; it delivers proven, practical tools and strategies that could help the industry not only meet today's manufacturing demands, but also future-proof plant design and operations for the rapid evolution of cell therapies. Attendees of this presentation will gain a potential roadmap for modernizing cell therapy manufacturing and a toolkit for production challenges—positioning companies to deliver better therapies, more efficiently, to more patients.

To learn more about the 2025 ISPE Annual Meeting & Expo, see the full agenda at ISPE.org/conferences/2025-annual-meeting-expo

About the author

Ciby Abraham, PhD, Senior Director and Group Manager of Project and Product Leadership in CMC Regulatory Affairs at AstraZeneca, previously served as a review chemist and quality lead at the US Food and Drug Administration, and has held roles as a formulator, analytical method development scientist, and a manufacturing specialist in the pharmaceutical industry. Abraham holds a PhD in chemistry from Johns Hopkins University, a master's degree in chemistry from St. John's University, and a bachelor's degree in chemistry from Binghamton University. An ISPE member since 2020, he is serving as the 2025 ISPE Annual Meeting & Expo Conference Chair.



ISPE Assists Health Canada with ICH Q13 Guidance Training

By Christopher J. Potter, PhD

ISPE successfully assisted Health Canada with International Council for Harmonisation (ICH) Q13 implementation training in virtual sessions with 170 participants.

Continuous manufacturing has been used for decades across various industry sectors. Some common pharmaceutical manufacturing unit operations like tableting and automated liquid filling are inherently continuous but often run in batch mode due to limited input material. Interest in fully continuous pharmaceutical manufacturing—linking operations like powder granulation and tableting—emerged in the early 2000s, aiming for regulatory approval. Progress followed, with the first regulatory approval for continuous granulation in 2015 [1], and additional product approvals in 2016, 2017, 2018, and 2020 [2].

Although literature reports indicated that the early product approvals were accepted in many regions [1], individual regions started to draft guidelines between 2016 and 2019. A proposal was made and accepted by the ICH in a concept paper in November 2018 as ICH Q13 "Continuous Manufacturing of Drug Substances and Drug Products" with the aim of introducing a harmonized guideline to facilitate global introduction of continuous manufacturing. An expert working group was established that produced a Step 2 draft document for public comment in July 2021.

A finalized guideline was issued in November 2022 [3]. This guideline describes scientific and regulatory considerations for the development, implementation, operation, and life cycle management of continuous manufacturing. Building on existing ICH Quality guidelines, this guideline provides clarification on continuous manufacturing concepts and describes scientific approaches and regulatory considerations specific to continuous manufacturing of drug substances and drug products. A comprehensive set of training videos was issued in November 2024 [4]. The guideline is in the process of implementation by ICH member regulators.

ISPE's Product Quality Lifecycle Implementation (PQLI)® initiative was created to provide guidance on practical implementation of the concepts described in ICH guidelines, focusing initially on Q8, Q9, Q10, and Q11. These guidelines promote enhanced science- and risk-based approaches to product development, technology transfer, and manufacturing, with the goal of fostering innovation and continuous improvement. One such innovation is the adoption of continuous manufacturing in the pharmaceutical industry.

Under the PQLI® umbrella, a continuous manufacturing team [5] was established in 2017 to develop a body of knowledge supporting global implementation of continuous manufacturing. Over the past three years, the team has:

- Published seven articles on continuous manufacturing
- Conducted an Expert Exchange webinar
- Responded to the ICH Q13 Step 2 draft guideline with a series of well-constructed technical comments, many of which were incorporated in the final Step 4 document
- Drafted an ISPE Good Practice Guide on control strategy development for continuous manufacturing, scheduled for release later in 2025.

IMPLEMENTATION OF ICH Q13 IN CANADA

After the final ICH Step 4 document was issued, the ICH Q13 Implementation Working Group (IWG) continued to work to produce training material. During preparation of the ICH training material, Health Canada approached ISPE to assist with the implementation based on the positive experience with previous ISPE training for ICH Q12 implementation [6]. Health Canada's request was to establish ISPE's interest in providing some industry virtual sessions for their staff to understand industry perspectives as well as potentially facilitating some visits to manufacturing sites.

Leadership of ISPE's PQLI® and Continuous Manufacturing teams interacted with Health Canada's small and biological molecule review leadership to establish requirements and timescales. Given that this virtual training would complement the ICH training material, there was sufficient time to develop the agenda and prepare material using industry case studies and highlighting industry "pain points." Consequently, ISPE agreed to form a Q13 Training sub team to deliver the training and take account of ICH training material.

During discussions between Health Canada and ISPE it was agreed that invitations to this virtual training could be made to other regulatory agencies. For the training itself, invitations were sent to 16 UK Medicines and Healthcare products Regulatory Agency (MHRA) quality reviewers, three UK MHRA inspectors, and four Singapore Health Sciences Authority (HSA) reviewers. The Q13 training was conducted in four half-day sessions. ICH Q13 was implemented in Canada earlier this year.

The training agenda was jointly developed by senior small molecule and biologics reviewers from Health Canada and ISPE's PQLI® and Continuous Manufacturing teams. The training aimed to prepare Health Canada assessors and inspectors for ICH Q13 implementation by deepening their understanding of

industry practices in continuous manufacturing, sharing real-world challenges to encourage dialogue with regulators, offering flexible, on-demand access for participants with varying expertise, and aligning with ICH IWG training efforts.

While continuous manufacturing of biologics is less advanced than for small molecules, industry requested inclusion of case studies—particularly on monoclonal antibody production—to reflect current experience.

Training combined presentations, Q&A, and listen and learn sessions using case studies and published industry materials. Case studies—covering process dynamics, control strategy, and disturbance handling—were developed for both small and biological molecules. Each session included a plenary presentation followed by breakout discussions with pre-set questions, culminating in a final Q&A.

The remote training, delivered via Microsoft Teams, reached ~170 Health Canada reviewers and inspectors, with notable participation from MHRA and HSA. ISPE experts from the US and EU led plenary case study presentations and chaired the program. Participants joined from Canada, the UK, and Singapore. Breakout groups, leaders, and rapporteurs were preassigned, and the sessions were effectively facilitated by Health Canada.

Formal feedback is being collected and will be analyzed. Early responses indicate strong engagement and praise for the clear, high-quality presentations. ISPE thanks Health Canada for the opportunity, their input on program design, and expert facilitation.

Special thanks go to the training group members and their companies for their time and materials. Participants agreed the training was successful and met its objectives.

References

1. Almaya, A., and K. Boue. "Regulatory Aspects of Global Acceptance of Continuous Manufacturing." *Pharmaceutical Engineering* 41, no. 4 (July/August 2021):30–4.
2. Giacoletti, K. and W. J. Roth. "Continuous Manufacturing as a Tool for Accelerated Development." *Pharmaceutical Engineering* 41, no. 4 (July/August 2021):22–9.
3. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Tripartite Guideline Q13: Continuous Manufacturing of Drug Substances and Drug Products. Final Concept Paper." Final Version. Published 16 November 2022, https://database.ich.org/sites/default/files/ICH_Q13_Step4_Guideline_2022_1116.pdf
4. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Q13 Training on Continuous Manufacturing of Drug Substances and Drug Products." www.ich.org/page/quality-guidelines
5. International Society for Pharmaceutical Engineering. "Product Quality Lifecycle Implementation (PQLI)®." https://ispe.org/initiatives/pqli
6. Potter, C. J. "ISPE Team Assists Health Canada with Training on ICH Q12 Implementation." ISPE iSpeak Blog. 2 June 2022. https://ispe.org/pharmaceutical-engineering/ispeak/ispe-team-assists-health-canada-training-ich-q12-implementation

About the author

Christopher J. Potter, PhD, is a chemistry, manufacturing, and controls (CMC) pharmaceutical consultant. He began his career as a research scientist over 50 years ago for Beecham Research Laboratories, eventually accepting senior roles with AstraZeneca in analytical development, research and development quality assurance (R&D QA), project management, CMC documentation, and as director of external pharmaceutical programs. He is a member of numerous ISPE committees. He joined ISPE in 2007.

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CELESTE FRANKENFELD LAMM, PHD

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Celeste Frankenfeld Lamm encourages young professionals to identify and pursue the aspects of their jobs they feel passionate about, "The things that get you out of the bed in the morning tend to be the areas where you are going to perform strongly. Once you've identified them, it's important to make your own opportunities. Let leadership know your work passions, express interest in teams or initiatives that will enable you to build upon those strengths, and frame it in light of how your interest can benefit the on-going work in your company or institution." Following her own advice led her to her current role as Senior Director, Lead of the Chemistry, Manufacturing, and Controls (CMC) Policy team, with responsibility to both the Quality and Global Regulatory Affairs organizations at Merck & Co.

She is responsible for a two-way exchange of CMC policy information between the external environment and internal stakeholders, monitoring trends to identify potential impact on products and processes to support planning and compliance, as well as developing policy proposals to share with regulators and industry groups to shape future guidelines. Lamm holds a bachelor's degree in chemistry and biology from Greenville University, and a doctorate in pharmaceutical chemistry from the University of Kansas. She currently serves as Co-Chair of the ISPE Product Quality Lifecycle Implementation (PQLI®) committee, is a member of the PQLI® Transportable/Point of Care and PQLI® Patient Centric Specifications/ICHQ6 technical teams, the Regulatory & Quality Harmonization Committee (RQHC) APAC Regional Focus Group, and the ISPE Regulatory Steering Council.

HOW DID YOUR CAREER JOURNEY UNFOLD?

I started my career as an analytical scientist. As part of my role, I helped submit the specifications we had developed. When we received pushback from the regulators, I wanted to engage more closely with them and share my perspective of why I thought these were appropriate specifications and wanted to understand from their perspective why they had concerns. I transitioned into a regulatory role because it was something I was passionate about. And then I took on a more external role so that I could converse with regulators on a more regular basis.

WHAT DO YOU ENJOY MOST ABOUT YOUR WORK?

I love the people I get to work with, and the fact that the department I work in is global. Outside of my company I enjoy working with regulators and people in the pharmaceutical industry. It's powerful to be able to pull together the different perspectives and find solutions. A key component of policy work is identifying a problem; in my case, a gap or barrier to product innovation in a guideline and working with others to fix it. It is wonderful to have the opportunity to hear diverse opinions and perspectives.

WHAT IS A PROJECT YOU'RE PROUD OF?

Recently I worked with a group of scientists from ISPE's PQLI® team to deliver training to Health Canada on ICH Q13. In addition to Health Canada, we had attendees from the UK's Medicines and Healthcare products Regulatory Agency (MHRA) and Singapore's Health Sciences Authority (HSA). It took a lot of work and a lot of coordination across different companies, but it was rewarding in multiple ways.

The training was well received. We had breakout sessions where we talked with regulators and inspectors, allowing us to hear their questions and share how we envision implementing Q13 within our companies, including our use modeling for continuous manufacturing. What was unique about this training was that we had the chance to share the information with a large number of regulators, as opposed to just a small team.

WHAT DO YOU ENJOY ABOUT BEING A MEMBER OF ISPE?

Engaging with the people. I think that ISPE brings together so many brilliant minds, which has strengthened me as a CMC scientist and policy lead. I've had the opportunity to learn from so many people across many walks within the pharmaceutical industry—that has been the greatest benefit.

Currently, I'm working on a platform paper with several different members, bringing together diverse viewpoints from across the industry. There are a lot of questions about platform technology and how it can be applied, and it's been rewarding to collaborate with these individuals and hear their ideas.

— Marcy Sanford, ISPE, Production Manager

VOLUNTEER
PROFILE



NINA S. CAUCHON, PHD

PRODUCT QUALITY LIFECYCLE IMPLEMENTATION (PQLI)® COMMITTEE CO-CHAIR

Nina S. Cauchon is Director Regulatory Affairs (RA) Chemistry, Manufacturing, and Controls (CMC) at Amgen Inc. where she leads RA-CMC advocacy and external engagement. She has experience leading both early phase and commercial programs, including small molecules and biologics. Her areas of interest are regulatory challenges for innovative modalities and emerging technologies, CMC aspects of expedited review pathways, regulatory harmonization, and science and risk-based approaches to regulations. Cauchon is interested in working to change the paradigm for regulatory submissions using automated authoring and cloud-based collaborative reviews.

She is active in several external organizations which have helped her to build a strong network and knowledge base, including being a speaker and committee member for ISPE, California Separation Science Society (CASSS), Product Quality Research Institute (PQRI), American Association of Pharmaceutical Scientists (AAPS), International Consortium for Innovation and Quality in Pharmaceutical Development (IQ), and Drug Information Association (DIA). In addition to serving as the ISPE PQLI® Co-Chair and a member of the Regulatory Steering Council (RSC), she has been a member of the ISPE International Board of Directors (2020-2024), the PhRMA Global Quality and Manufacturing group, and the ICH Q2(R2)/Q14 Expert Working Group. She has a PhD from Purdue University School of Pharmacy and has over 25 years of industry experience.

HOW DID YOUR CAREER JOURNEY UNFOLD?

My first job was at Warner-Lambert/Parke-Davis in Morris Plains, NJ, as an analytical chemist, then I moved to California and worked at a small start-up in Santa Barbara, before joining Amgen in 1998 where I started out in analytical development supporting pharmaceutics and process development. About 12 years ago, I joined Regulatory Affairs- CMC. Because I had worked on filings and submissions to regulators as part of my technical role, I thought it would be interesting to see it from the other side.

My current role in advocacy and external engagement involves a lot of outreach and one of the first organizations that I got involved with was ISPE. I joined the PQLI® accelerating product development team and was very impressed because of how the group worked together to write articles and was really trying to create useful information to educate people around the world. It's really great to see the global outreach of ISPE and that sense of a common purpose and mission to help patients around the world.

WHAT DO YOU SEE NEXT FOR THE INDUSTRY?

The pace of change is so fast these days and with the amount of knowledge in the world growing exponentially, it can be hard to keep up. I think that regulators around the world have recognized the value of collaboration and reliance mechanisms as a means to gain efficiency. There is more work-sharing and collaboration using IT platforms where different regulators can view the same submission and collaborate on what their responses are going to be back to the sponsors. Not only is it more useful for regulator assessments, but it also has the advantage of being able to speed up those approvals for sponsors. It can also foster harmonization and innovation through building a common understanding of the requirements for the Quality/CMC sections of a regulatory submission. Together with these common platforms, automation of regulatory submissions using structured data and AI will free up scientists and product teams to really concentrate more on what the data is telling us, as it will enable reuse of information across sections without the manual labor of cutting and pasting.

WHAT DO YOU ENJOY ABOUT BEING A MEMBER OF ISPE?

The pharmaceutical industry is rapidly evolving, driven by technological advancements, regulatory trends, and global considerations. ISPE is well-positioned to assist its members in this changing landscape. ISPE's PQLI® initiative serves drug manufacturers and health authorities by providing tools and education to bridge the gap between regulations and implementation to achieve quality throughout the product lifecycle for the benefit of patients. It is at the nexus of science and regulation where scientific innovation meets regulatory expectations. We share strategies for translating regulations into practice, including detailed interactive training sessions for regulators. The teams have developed webinars, conference sessions, workshops, publications, and blog articles illustrating the practical implementation of new technology and regulatory approaches based on sound scientific, engineering, and business principles.

— Marcy Sanford, ISPE, Production Manager

Meet the ISPE STAFF



AMANDA BANNINGA

Hometown: Macomb, IL

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Amanda Banninga, Program Manager, Conferences & Digital Engagements.

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

As one of the Program Managers on the Conferences & Digital Engagements team, I am responsible for the management of ISPE's Facilities of the Future Conference, Europe Annual Conference, and Annual Meeting & Expo. I work closely with our dedicated volunteers who serve on the Program Committees of these conferences as they develop the educational content for each event, and I collaborate with stakeholders from almost every ISPE team as we work together to plan and promote the conferences.

Each conference takes more than a year to plan, so I am always working on different stages of each conference. I may be working on a call for proposals for one conference on the same day that I am reviewing the livestream platform for another conference. Or I might be providing feedback to our Marketing and Communications team for materials for one event while being on-site at another.

What do you love about your job?

I love being part of an organization that truly functions as a team. The staff and volunteers at ISPE are incredibly supportive of each other, and this helps us achieve our common goals.

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

I have a background in theater, and the arts are still very important to me. I sit on the board of a local arts organization that supports arts education and youth access to live performances. I also enjoy reading, and I love to spend time outside gardening and hiking.



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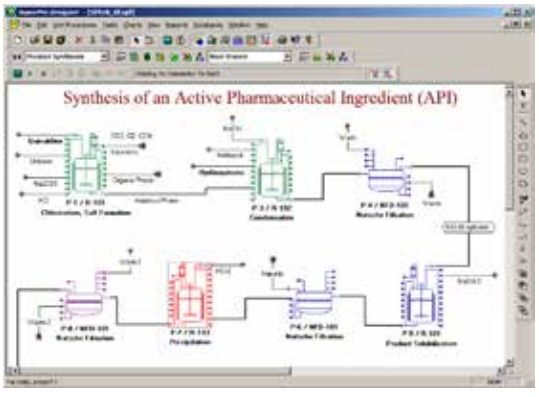

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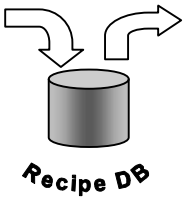

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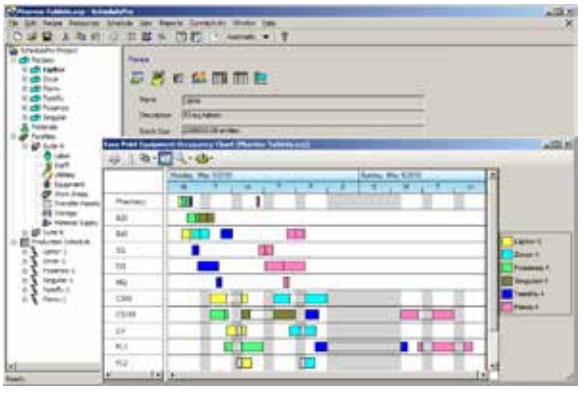

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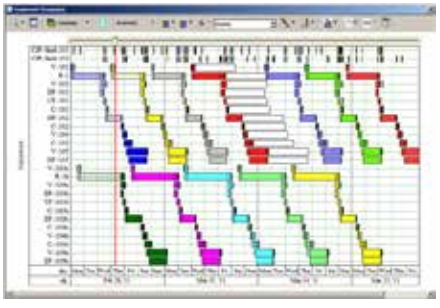

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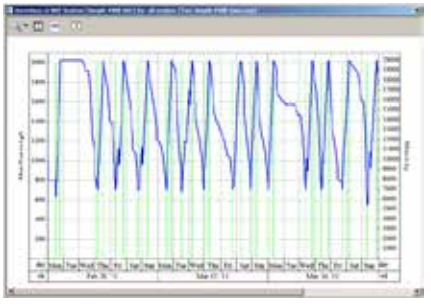

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