PHARMACEUTICAL ENGINEERING®

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FOCUS on Regulatory Trends/Quality Initiatives

A Vision for ICH Q12: Current Experience, Future Perspectives

ICH Quality Guidelines: Present Initiatives and ISPE Involvement

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By Joanne R. Barrick, RPh


Joanne R. Barrick, RPh

The Greatest Spectacle in Pharma

I live in Indianapolis, Indiana, truly a great place to live. It is not difficult to understand why I like Indy so much: humble, down-to-earth people, farming (I grew up on a farm), readily available participant sports, and many spectator sporting event opportunities including football, soccer, baseball, and racing. Especially during the month of May, racing and the Indy 500 in particular are spectacular. I "attended" my 27th or so race in person in 2020 (sitting outside the fence and watching on the big screen) and there is never a year when goose bumps don't raise on my arms as the 33 fastest oval track race cars in the world scream to the start in three-wide formation. The Indy 500 is held on Memorial Day weekend and there are many associated meaningful traditions. It is no surprise the race is referred to as the Greatest Spectacle in Racing.

I know many of you feel like you have been racing all year—some without leaving home—and the 2020–2021 course has included difficult twists and turns, but the results have been amazing. Congratulations to all of pharma for unprecedented speed in development, manufacturing, and distribution of high-quality COVID-19 vaccines and treatments, and for enabling us to start once again participating in the opportunities we love.

REGULATORY SPEEDS UP

We see speed in recent regulatory trends as well. As of 1 November 2020, the FDA had issued 60 new COVID-19-related guidances. ICH Q12 affords us the realization of many flexibilities outlined in ICH Q8 and supports efficient implementation of manufacturing and analytical innovation. The pandemic has taught us we can do clinical trial steps in parallel, collaborate with regulators throughout the development process, and submit rolling submissions to increase speed of approval.

Knowledge management and appropriate implementation of quality risk management also enable speed by facilitating quicker, accurate decisions and knowledge and product transfers as outlined in ISPE's recently published *Good Practice Guide: Knowledge Management in the Pharmaceutical Industry*. ICH Q9 and appropriate application of risk management, as discussed at ISPE's 2021 Asia Pacific Pharmaceutical Manufacturing Conference, enable identification and efficient application of resources to mitigate and prevent potential manufacturing issues.

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ISPE'S FOCUS ON SPEED

The ISPE Strategic Plan also contains focus on speed. We strive to make technical information available to our members at the time it is most valuable (and relevant). This is often when concepts are new, when innovation occurs, and/or when new regulatory expectations are established. We have made significant progress with quicker publication of our guidance documents and concept papers, partially due to the Content Priorities plan, which reflects member input and has just completed its first update. The plan enables integration and coordination across all of our product delivery platforms, including *Pharmaceutical Engineering*®, guidance documents, training, conferences, and webinars.

The theme of speed is also reflected in the 2021 ISPE Annual Meeting & Expo. Keynote presentations include Robin Kumoluyi, VP and Chief Quality Officer at Johnson & Johnson, presenting on "Leading with Agility: How the COVID-19 Pandemic Was a Catalyst for New Collaboration and Innovation." Planned educational session presentations and topics include "Applying Warp Speed Lessons to the Next Manufacturing Facility," "Driving Efficiencies Through Continuous Manufacturing," "Pivoting to Multiple Product Platforms to Treat COVID," and "Discovery Mindset: Benefits to Patients through Fast Speed to Market."

Thanks to all of our members who have continued to volunteer during this fast-paced and, at times, chaotic year. In some of my other volunteer work, I feel like folks give what is left over, when and if convenient. But many ISPE volunteers give "off the top," the very best they have to offer, with the passion to help their colleagues and contribute to moving the pharma industry forward. THANK YOU!

The 2021 Indy 500 was the 105th running but with a 140,000-fan limit (40%) and I don't think I will ever have greater appreciation for the opportunity to attend the race. Forty-six-year-old Helio Castroneves (a fan favorite for many years) won the race in dramatic fashion passing Alex Palou with two laps to go, becoming one of only four drivers to win the 500 four times. It was indeed spectacular!

Is 2021 the greatest spectacle in pharma? I cannot think of a more impactful year in my lifetime, but I am confident the innovation and speed experienced this year will lead to many more exceptionally impactful years. Thank you for all that you do to support patients around the globe and please consider sharing your passion with a student or Emerging Leader. I look forward to seeing many of you at the upcoming ISPE Annual Meeting & Expo. Stay safe!

Joanne R. Barrick, RPh, is Advisor, Global Validation, Technical Services/Manufacturing Science at Eli Lilly and Company, and the 2020–2021 Chair of the ISPE International Board of Directors. She has been an ISPE member since 1998.

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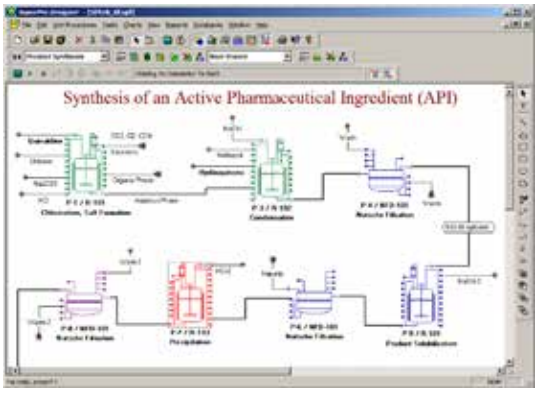

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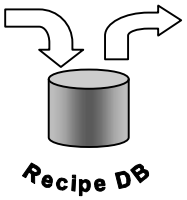

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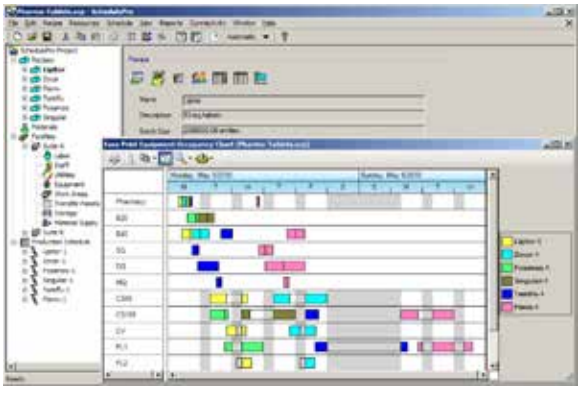

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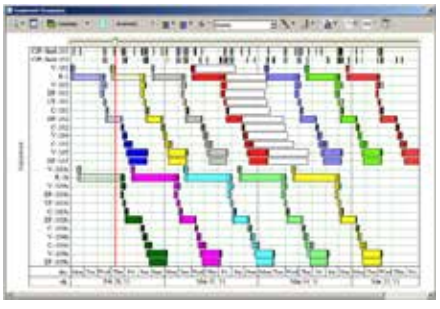

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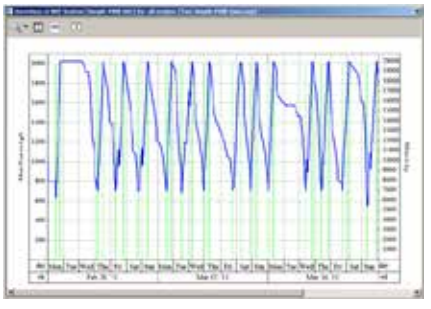

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John Clarke

PLANNING FOR FUTURE MEETINGS:
Face to Face or Virtual

Excitement for restarting face-to-face conferences is building and as plans at local and international levels are in progress, we continue to enjoy the benefits of remote interactions. Innovation and collaboration achieved through fully virtual conferences and seminars in the past year and a half show us that both have great benefits.

Some of my most memorable experiences with ISPE have been attending events held by the ISPE Ireland Affiliate. Local events were my introduction to ISPE and the workings of the Ireland Affiliate. Emerging Leaders (EL) events were a great way to meet peers working in manufacturing companies and service providers around Ireland and share experiences. The more active I became in organizing and attending these events, the more value I received. The wide range of events offered by ISPE means there is always opportunity to further specialize in a topic or learn something new.

GETTING STARTED

For students, recent graduates, and ELs, conferences give you a chance to make your way in the pharmaceutical industry. Attending informative talks by subject matter experts, visiting exhibitor halls, and socializing with other attendees provide experiences that develop your knowledge of the different disciplines and functions that contribute to a global supply chain of life-changing medicines. The people you meet and interact with have the potential to inform you on topics you may not be familiar with or guide your decision-making. As innovative modalities continue to be established, conferences provide an opportunity to stay at the cutting edge of what is possible in your career. Transformative changes are inevitable in the pharmaceutical industry and building a network with ISPE is a great way to get informed about the next manufacturing platform or regulatory expectation.

For ELs, ISPE meetings provide an opportunity to be in the room (virtual or face to face) with industry thought leaders and technical experts. Questions and conversations at conferences transcend geographies, disciplines, and job titles. They also bring ELs together to socialize and network, building relationships that will remain with them throughout their careers. While virtual formats have removed challenges for ELs to attend conferences and seminars, they offer a variation on the networking and collaboration that can be achieved in an in-person setting.

Historically, seminars and conferences have been opportunities to think out loud and discuss ideas. Their value in the pharmaceutical industry has always been in bringing manufacturing companies, regulators, researchers, and service providers together to discuss, speculate, innovate, and experiment in an informal setting. Ideas can be teased out through discussion, questions, and conversation, without needing to commit them to writing or publication. Fully digital conference platforms change this dynamic. While the informality of a face-to-face interaction or workshop can be difficult to replicate, digital conference platforms can ensure informal interactions take place.

HYBRID OPTIONS

Hybrid events have the potential to fulfill the benefits of virtual and in-person events. Roadblocks that previously restricted attendance of ELs such as travel costs have been removed through the virtual format. Innovative technical content can be enjoyed remotely and in your own time. For those who can attend in person, the benefits of a face-to-face interaction await. As ISPE has an amazing lineup of hybrid ISPE conferences planned for the end of 2021, I am looking forward to catching up with people in a new hybrid way.

Check out the upcoming conferences by visiting https://ispe.org/conferences

There has never been a better time to volunteer with your local ISPE Emerging Leaders Affiliate or Chapter. Please get in touch by visiting https://ispe.org/membership/volunteer

John Clarke is a Process Lead with Pfizer in Dublin, Ireland, and the 2020–2021 ISPE International Emerging Leaders Chair. He has been an ISPE member since 2014.

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 By Vivien Santillan


Vivien Santillan

Adapting Technology and Culture to Emerging Technologies

Innovation is generally associated with driving business outcomes and processes, adapting to technology, and developing creative management approaches. In the pharmaceutical industry, innovation takes on a more extensive and specific meaning. It is acknowledged to be continuous as it involves dynamic thinking on how to integrate technology into drug development, manufacturing processes, and business operations. It is also deemed critical as it must address the emerging needs of patients while maintaining product quality, efficacy, and safety.

With present-day circumstances and the pandemic affecting almost all sectors of society, the role of innovation in the pharmaceutical industry continues to be at the forefront of industry consideration. Advanced therapeutics medicinal products (ATMPs) and cell and gene therapy are technologies being developed and are the ways forward for most companies. Innovative and emerging technologies include big data and analytics, artificial intelligence (AI), augmented and virtual reality (AR/VR), internet of things (IoT), blockchain, machine learning, and 3D printing for personalized medicines. These technologies are also gaining traction to benefit not only the pharmaceutical industry, but society in general.

TECHNOLOGY AND INNOVATION

The use of technology is an enabler for innovation. Scalable technology consistently demonstrates a trend toward innovation to improve and complement existing processes. Acknowledge that the current ways of doing things might no longer be as effective and improvements are necessary to pave the way for innovation through the use, adaptation, and/or diffusion of relevant technologies.

Adapting technology and innovation requires strategic, organizational, and managerial decisions as well as investment in people and other resources. What could be current or mature for industrialized countries may not be so in emerging countries. An environment that promotes a culture of innovation encourages opportunities for continuous improvement and supports creative thinking for processes, products, and services development and enhancement. Thus, technology must not only be exploited for progressive purposes but also must be assimilated or integrated with an organization's culture and identity. Consequently, outputs and expectations will be achieved.

CULTURE CHANGE

How are innovation and technologies accepted by the rest of the world? How does one's culture, whether organizational or personal, affect the decision to adapt technology? Why does it take some time for some countries to innovate and implement technology? What is the impact of culture in technological innovation and adaptation?

The Women in Pharma® Mentor Circles initiated a collaboration with ISPE Affiliates through a quarterly webinar entitled "Emerging Technology for Upcoming Countries." The purpose is to discuss topics on technologies and innovation that emerging and upcoming countries have not yet adopted as well as related challenges, opportunities, and implementation. The novelty of this webinar series is the focus on how technologies are adapted with respect to culture and behavior. The webinars allow group discussions on how to position organizations for the future of life sciences. Every innovation and technological strategy needs highly talented, skilled, and motivated personnel. The series will provide ISPE Emerging Leaders and students the opportunity to learn and prepare themselves for emerging technologies. Pharmaceutical management will be able to identify skills gaps and strategize their organizations' innovation approach.

In cooperation with the ISPE India Affiliate, the mentor circle program was launched 28 June with participation from the Brazil, Mexico, Russia, Malaysia, Indonesia, Singapore, Australasia, Japan, Philippines, and Thailand Affiliates. The new WIP Mentor Circle program initiative schedules will be posted on the WIP page on the ISPE website and in *The Bridge* newsletter. Join us and share your experiences, expertise, and opinions on emerging technologies for emerging and upcoming countries.

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

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A Vision for ICH Q12: CURRENT EXPERIENCE, FUTURE PERSPECTIVES

By Jessica Lo Surdo, PhD, Nina S. Cauchon, PhD, Connie Langer, Saroj Ramdas, and Eli Zavialov, PhD

Management of global postapproval chemistry, manufacturing, and controls (CMC) changes is a growing challenge for industry with many issues. ICH Q12 (Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management) is a transformative document shaping global regulatory postapproval submissions [1] that will help alleviate some of these issues.

Regional regulations necessitate the development and maintenance of country-specific regulatory documents that contain different quality information for the same product to meet individual country requirements. In some instances, simultaneous operation of different manufacturing processes or redundant testing may also be needed for the same product to ensure its uninterrupted availability for patients in various global markets. Increased inventory segregation and the potential for errors in manufacturing and regulatory compliance as well as varied submission, review, and implementation timeframes add to the complexity in the oversight of global commercial product supply chains. Thus, different regulatory requirements around the world are currently a disincentive to making innovative changes or improvements to increase process efficiency and robustness.

The ICH Q12 guidance provides a framework to facilitate the management of CMC changes in a more predictable and efficient manner, building on the science- and risk-based approaches outlined in the prior ICH Quality Guidelines—ICH Q8(R2), Q9, Q10, and Q11. A well-established and effective company pharmaceutical quality system (PQS), in compliance with regional GMP requirements [2], is critical to achieve the full potential of the ICH Q12 concepts.

Postapproval changes can be categorized using risk-based principles and reported to regulatory authorities based on standardized terminology (prior approval, notification-moderate, notification-low) or not reported (i.e., documented within a company's PQS). Thus, increased product and process knowledge can contribute to a better understanding of which post-approval changes require a regulatory submission. Other key regulatory tools described in ICH Q12 include the following concepts:

- Established conditions (ECs): Legally binding information considered necessary to assure product quality. Changes to ECs require regulatory reporting according to the above standardized terminology. Supporting information is still required to accompany ECs.
- Postapproval change management protocols (PACMPs): These protocols provide predictability regarding the information required to support a change and the type of regulatory submission based on prior agreement.
- Product life-cycle management (PLCM) document: Central repository for ECs, reporting category for making changes to approved ECs, PACMPs (when proposed), and any post-approval CMC commitments.

This article provides a description of the current regulatory environment and status of ICH Q12 implementation at the time of writing. It also provides case studies from an industry perspective that serve as practical examples of how industry has interpreted ICH Q12 and has applied ICH Q12 tools to improve PLCM.

Table 1: Overview of current ICH Q12 implementation status in various regions [3].

Country/Agency	Current ICH Q12 Implementation Status*	Unique Considerations/Challenges	Reference
US FDA	ICH Q12 and Implementation Considerations Guidance published on the FDA website. The 2015 draft guidance on ECs was withdrawn.	Overall, the concept of EC is consistent with FDA regulations in 21 CFR 71 314.70(a)(1)(i), 314.97(a), and 601.12(a)(1).	5, 6
EU EMA	Note on ICH Q12 implementation guidance issued	Certain ICH Q12 elements such as ECs and PLCM document are not compatible with the current legal framework. Recently announced EU legislation revision initiative may change this and enable the use of all ICH Q12 tools.	7, 8
Japan PMDA	In progress	EC and PLCM document will need to be aligned with the Japanese Application Form. PACMP is a novel concept that requires the revision of existing legal framework (ongoing).	9, 10
Canada (Health Canada)	In progress	EC and PLCM will need to be aligned with the Canadian Certified Product Information Document (CPID). There has been limited experience with PACMPs so far.	11
Brazil ANVISA, China NMPA, Korea MFDS, Singapore HSA, Switzerland Swiss Medic, Chinese Taipei TFDA, Turkey TITCK	In progress	Many countries have initiated pilots and consultations in order to get more insights into ICH Q12 concepts, define implementation approaches, and revise the underlying legal frameworks.	3

*Status according to ICH Q12 website (https://www.ich.org/page/quality-guidelines).

CURRENT ADOPTION BY GLOBAL REGULATORS

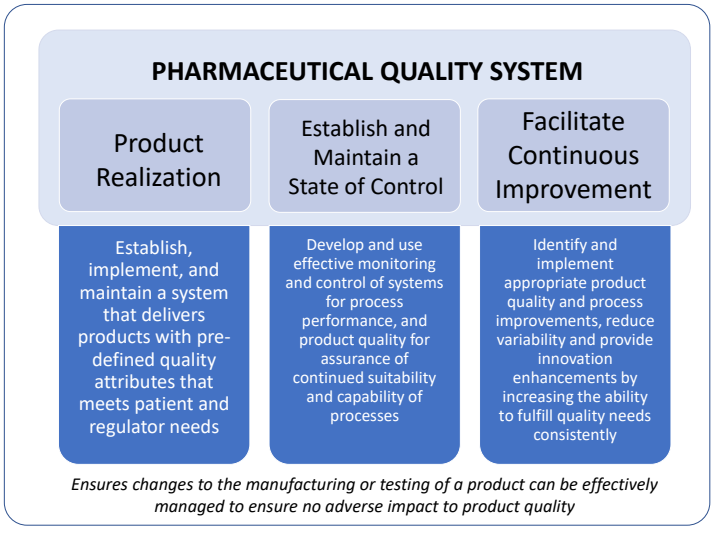
The final draft of ICH Q12 was adopted by the ICH Assembly in November 2019 (Step 4), and the guideline is now in Step 5, with regional implementation efforts in progress as summarized in Table 1 [3]. The ICH Implementation Working Group (IWG) was established to develop a comprehensive training program to "facilitate an aligned interpretation and a harmonized implementation of ICH Q12 in ICH and non-ICH regions." [3] According to the ICH website, the current ICH Q12 IWG work plan foresees the completion of training program preparation later this year, followed by the initiation of training activities in late 2021 [4].

The European Medicines Agency (EMA) was one of the first global health authorities to adopt ICH Q12 in January 2020 and to issue its implementation guidance in March 2020 [8]. Despite the extensive discussions and negotiations during ICH Q12 development and endorsement, the incompatibilities between certain concepts in ICH Q12 and the existing EU legal framework (e.g., the Variations Regulation (EC) No 1234/2008) could not be fully resolved, preventing the full implementation of ICH Q12 in the EU.

EMA's implementation guidance emphasizes that "the legal framework always takes precedence over technical and scientific guidelines"[7], which means that one must always default to the requirements laid down in the current EU Variations Regulation and associated EU Variations Guidelines. As such, scientific risk-based approaches to defining ECs and associated reporting categories, as described in Chapter 3.2.3, and the PLCM document, as described in Chapter 5 of ICH Q12, cannot be currently applied in the EU until the legal framework is revised. However, other ICH Q12 tools and enablers, such as quality risk-based postapproval change reporting categories using PACMPs, are considered compatible and ready for implementation. Recently, it was announced that the European Commission has launched the process for revision of the EU's pharmaceutical legislation, issuing a "combined evaluation roadmap/inception impact assessment" [7]. One of the stated goals of this revamp includes an attempt to address the "inefficiency and administrative burden of regulatory procedures" in order to achieve the "simplification and streamlining of procedures and internal processes to reduce timelines and regulatory burden."[7]

The US FDA published the final ICH Q12 guideline and annexes on its website in May 2021 [5]. This guidance is replacing the draft 2015 FDA Guidance on Established Conditions, which accordingly has been removed from the FDA website. In addition, the FDA has issued a draft guidance with specific considerations around the ICH Q12 implementation, which complements ICH Q12 and clarifies "how the ICH Q12 tools and enablers can be implemented within the US regulatory system" [6]. The guidance reflects key lessons learned from the 2019 FDA Pilot on Established Conditions [12], providing detailed recommendations on how to define, submit, and maintain the proposed ECs. It also clarifies the relationship between ICH Q12 PACMPs and FDA comparability protocols, explains how to translate ICH Q12 postapproval change reporting categories to

Figure 1: Overview of Amgen's PQS.



the existing FDA supplement categories, and illustrates the use of a PLCM document with specific examples.

In Japan, the PMDA has established an internal working group to facilitate the implementation of ICH Q12. One of the interesting aspects that will need to be addressed is the relationship and any opportunities for alignment between the Japanese Module 1 Application Form that contains the "approved matters" and the ICH Q12 concepts of ECs with associated reporting categories and PLCM document. Regarding PACMPs, there is currently no similar concept in Japan and therefore, a change in the national regulations will be required to implement it. Japan has taken a proactive approach to gaining experience with PACMP, with MHLW/PMDA starting a pilot program for PACMP in April 2018 prior to ICH Q12 reaching Step 4 [10]. A PACMP mockup that reflected the contents of the Application Form for Japan was created [9]. Following the pilot, the PACMP was introduced into the regulation as the "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" and will come into effect in 2021.

Health Canada has announced its target timeframe for implementation of ICH Q12 to the second half of 2021 to "allow sufficient time for the preparation of regulators and stakeholders" [11]. Toward that goal, Health Canada planned to launch stakeholder consultations in 2021 to gather feedback on the final elements of the implementation of the Q12 guidance in Canada. Similarly, in Japan there are some opportunities for alignment of the Canadian CPID with the ICH Q12 concepts of ECs and PLCM document, as well as more widespread acceptance of PACMPs.

INDUSTRY PERSPECTIVES

The stage of ICH Q12 implementation varies across both global health authorities and industry. Industry engagement with regulators on adoption of ICH Q12 concepts and the extent of internal adoption of ICH Q12 concepts within an individual company's own PQS framework have shaped industry experience and perspectives. Several companies participated in the FDA's Established Conditions Pilot Program as an opportunity to engage with the FDA in defining and proposing ECs. The pilot program provided the FDA with an opportunity to engage with sponsors and gain practical experience in (a) assessing proposed ECs, (b) engaging with applicants during the review to refine proposed ECs, (c) ensuring assessment decisions can be made without impacting user fee timelines, and (d) identifying agreed-upon ECs at time of approval [12]. Experiences with the pilot program varied widely across industry participants, and sponsor perspectives are summarized below where applicable.

Amgen

Amgen focused on a drug product container closure change for a biologic molecule as part of the FDA ECs Pilot Program. Amgen used an enhanced approach as described in ICH Q12 to propose ECs and corresponding reporting categories in a PLCM document. The enhanced approach was based on an understanding of the interaction between process inputs and quality attributes of the molecule. Proposed reporting categories for ECs were based on process and product knowledge, as well as Amgen's established PQS utilizing a risk-based approach.

Proposed reporting categories for ECs were based on (a) potential risk to product quality, (b) experience in changing the proposed EC, and (c) capability of PQS in managing changes and an effective continued process verification (CPV) to provide ongoing assurance the process remains in a state of control. Amgen's PQS was defined in the PLCM document to address several key quality process elements, including those necessary for ICH Q12 implementation. Amgen's PQS can appropriately identify and mitigate risk, develop robust plans for change implementation, and can effectively assess impact to product quality (Figure 1).

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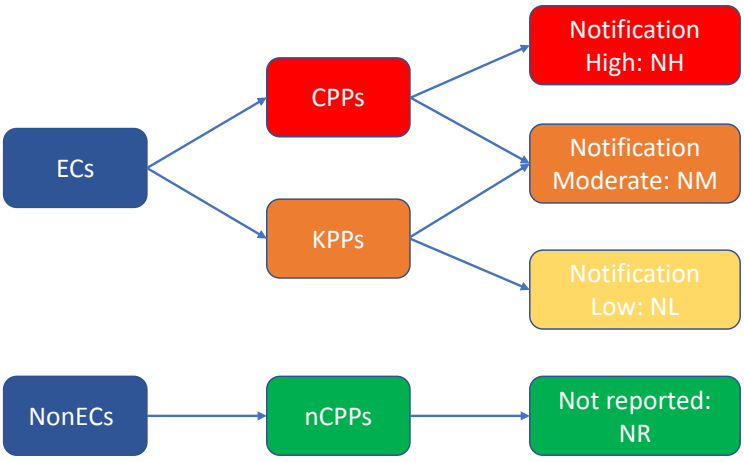
Figure 2: Overview of Janssen's approach to define ECs for manufacturing process parameters.



The initial scope of the change included a drug product primary container closure change with no modification to drug product formulation. ECs and corresponding reporting categories were therefore assessed for the relevant drug product sections of the dossier. A team of cross-functional subject matter experts (SMEs) assessed ECs, which were filed as a PLCM document in 3.2.R (regional section of Module 3). For changes with any potential risk to product quality, Amgen assigned ECs and associated reporting categories in a tiered approach based on risk severity. NonECs were also described in the PLCM document to define supportive information that would solely be managed by the PQS. Amgen is actively pursuing engagement with FDA and other health authorities to realize the full potential benefit of ICH Q12.

Janssen

Janssen's initial approach around the implementation of ICH Q12 has focused on manufacturing process descriptions for conventional small molecule solid oral dosage forms. As the global health authority expectations around the level of detail provided for process parameters (critical and noncritical) in manufacturing process descriptions continue to increase [13], Janssen has sought to leverage key ICH Q12 enablers such as ECs to mitigate the increase in the level of process parameter details in regulatory filings and reduce the potential postapproval change reporting burden.

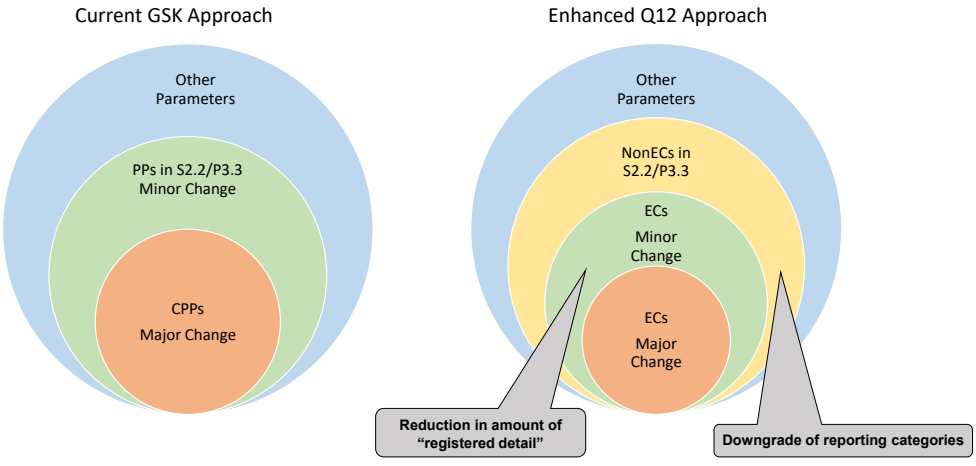
To achieve that goal, the first step was to develop a more granular risk assessment and filtering tool that would permit moving beyond the current binary critical process parameter (CPP)/noncritical process parameter (nCPP) paradigm and provide a clear framework for determination of ECs and associated risk-based reporting categories for all process parameters using the enhanced approach. A third category of key process parameter (KPP) was introduced for internal use only and defined by Janssen as parameters of the manufacturing process that may have a relationship to a CQA but have a reduced risk of impacting the safety or efficacy of the product compared to a CPP. Each functional area could then further refine and elaborate this general definition in terms of what "reduced risk" means in practice in their area, as well as to propose further risk filtering and ranking of CPPs and KPPs based on the degree of their impact on CQAs and the overall control strategy.

For example, for drug substance synthesis, process parameters impacting an impurity observed at intermediate stages but not in the final drug substance can be considered as KPPs. For the drug product manufacture, in cases where the primary CQA control strategy is focused on unit operation outputs (e.g., in-process controls [IPCs] or output CPPs), the input process parameters that directly influence these outputs may be defined as KPPs. Finally, each risk-based category of process parameters was mapped to the appropriate postapproval reporting category (Figure 2). It is important to note that not all process parameters in the same criticality category (e.g., CPPs) are necessarily assigned to the same reporting category (e.g., notification-high), as this assignment depends on the actual risk to quality and can depend on the nature and directionality of the change (e.g., expanding versus tightening of control ranges), the ability to control a given parameter within its operating range, and the overall control strategy (e.g., the presence of other downstream control elements). Janssen is currently piloting this approach in select markets and plans to refine and adjust it based on the feedback received.

GSK

GSK's preparation with regard to ICH Q12 includes a global cross-modality team supporting adoption and implementation of ICH Q12 principles and tools by leveraging current quality by design (QbD) practices and a robust PQS. Participation in the FDA ECs Pilot Program provided an opportunity to gain feedback

Figure 3: ICH Q12 impact on manufacturing process description.



from the agency regarding GSK's strategy for identification of manufacturing-process-related ECs. GSK submitted a prior approval supplement (PAS) to support a column-size diameter change for a chromatography unit operation of a mAb. The science- and risk-based approach utilized by GSK was based on the failure modes effects analysis (FMEA) technical risk assessment evaluating criticality of the parameters and controls. EC identification was based on the severity scoring regarding the impact to CQAs. The strategy utilized a continuum approach where (a) a high severity score (i.e., extremely severe, moderately severe) was identified as an EC, (b) a low score (i.e., not severe) was defined as a nonEC, and (c) a medium score (i.e., slightly severe) required additional assessments to determine if it was an EC or nonEC. Further assessments for slightly severe were based on product and process knowledge (i.e., process characterization data). If process characterization data demonstrated a parameter or control did not have a practical impact on a CQA over a reasonable range, it was considered a nonEC. However, if knowledge and data were not available to assess the impact, it was classified as an EC until further information would be available. Following the EC identification exercise based on the continuum approach, 21 registered criteria were reduced to seven criteria defined as ECs, whereas the remaining 14 criteria were defined as nonECs to be managed under the PQS.

ICH Q12 provides an opportunity to reduce registered detail requiring regulatory action while providing regulators the necessary transparency to review a product's process as illustrated in Figure 3. The enhanced Q12 approach will provide an opportunity to clearly define ECs requiring regulatory action and potentially downgrading regulatory reporting categories for others. This leads to relevant information of ECs and nonECs to be included in the Module 3 CTD sections S.2.2 and P.3.3 when the enhanced ICH Q12 approach is implemented. GSK continues to advance adoption of ICH Q12 tools to support applications in markets as Q12 implementation evolves globally.

Pfizer

Pfizer used an enhanced approach as described in ICH Q12 [1] to propose ECs and corresponding reporting categories in a PLCM document that included ECs across the full scope of Module 3. The PAS submission was submitted as part of the US FDA Office of Policy for Pharmaceutical Quality's ECs Pilot Program [12]. Pfizer's science- and risk-based approach was based on rigorous risk assessments, overall control strategy, process understanding, product knowledge, enhanced analytical method development, and a robust PQS [14].

The small molecule active ingredient synthesis included robust starting material controls and multiple in-process controls to ensure drug substance quality. A safety-based approach was used to determine reporting categories for specification ECs to support the overall control strategy. The drug product used compendial excipients, direct compression, and a standard tableting process. The analytical methods to assess the drug substance and drug product included six different procedures for which ECs were based on the method principle, method-specific performance criteria (i.e., validation criteria per ICH Q2 [15]), and higher-level method parameters [14].

A comparison of the reporting categories in the PLCM versus current FDA guidance [16] revealed several instances where the PLCM and the guidelines are aligned, as well as many ECs that have reduced reporting categories. The latter are summarized in Table 2.

ICH Q8–Q11 provided the framework for science- and risk-based approaches; however, technical and regulatory gaps prevented the realization of postapproval flexibility. ICH Q12 provides the needed regulatory framework, and by leveraging the concepts therein [1], the approved PLCM increases flexibility and enables continual improvement of the product [14]. Pfizer is currently exploring opportunities to implement ICH Q12 tools in global registration applications.

Table 2: Summary of reduced reporting categories reviewed and approved in the PLCM.

Drug Substance Manufacturing Process	Drug Product Manufacturing Process	Analytical Performance	Specification
• Omission of recrystallization from the manufacturing process reduced from PA to NM. • Changes to 8 CPPs reduced from PA to NM. • Changes to 3 PPs that have very low risk to impact quality attributes reduced from NM to NL. • Changes to 24 noncritical process parameters in Steps 1 and 2 reduced from NM to NR. • Changes to 18 noncritical process parameters in the final step reduced from PA to NR.	• Changes to the equipment using the same design and operating principle reduced from NL to NR. • Changes to tablet weight and film-coating IPCs reduced from NM to NL. • Changes to screen aperture will be reduced from PA to NL.	• Changes to method principle and performance criteria will be reported as PA. • Changes to 35 higher-level operational parameters (e.g., solvent system for HPLC) and the system suitability criteria will be reported as NM (no reduction). • Change to 6 slightly more detailed parameters (e.g., the wavelength of the analysis) reduced from NM to NL. • Changes to 65 parameters reduced from NM to NR.	• Safety- and risk-based approaches were used to define reporting categories for raw materials critical IPCs and intermediateand drug substance specifications.

FEEDBACK ON IMPLEMENTATION PROGRESS

As individual companies have begun to implement ECs and ICH Q12 concepts, it has become clear that there is some divergence in approaches and associated terminology that have been communicated to health authorities. Recent engagements between industry leads and health authorities have highlighted key issues faced by regulators and sponsors in implementing ICH Q12, and defined a potential path to a more harmonized approach to postapproval change management in the future.

One of the key challenges emphasized during the 2021 ISPE Challenges and Success of ICH Q12 Related Submissions webinar [17] was associated with the importance of robust criticality assessments and effective communication of results and data to regulators in support of the proposed ECs. Most of the companies surveyed have relied on the enhanced approach as defined in ICH Q12. Many companies have also found it necessary to update their risk assessment processes to be able to justify the appropriate reporting categories for those process parameters where a quality impact cannot be ruled out. Some companies have found it useful to introduce an additional intermediate criticality category of a KPP, while others employed "criticality continuum" approaches (e.g., based on a severity assessment) without introducing the KPP concept. Future alignment of terminology across industry will help improve consistency, as well as strike the appropriate balance in providing a sufficient level of detail in the dossier while maintaining life-cycle flexibility [18].

FDA perspectives highlighted during the ISPE ICH Q12 webinar were in line with issues facing industry related to ICH Q12 implementation. Regulators emphasized the importance of effective and clear communication where "a shared understanding of the applicant's intent, scope, and nomenclature is essential [18]." The key takeaway from the FDA pilot experience was the varying approaches taken by applicants, with emphasis on the complexity of proposals put forth by sponsors often exceeding examples outlined in ICH Q12. Challenges related to existing products that were developed prior to ICH Q8, and therefore prior to formal criticality assessments for process parameters, provide an opportunity for ICH Q12 to address gaps associated with legacy products. To holistically address these challenges, FDA adoption and concurrent draft guidance for considerations in implementing ICH Q12 are currently in progress.

Industry participants had the opportunity to ask questions and provide live feedback to the presenters during the ISPE webinar. Seven key areas were identified as topics of interest:

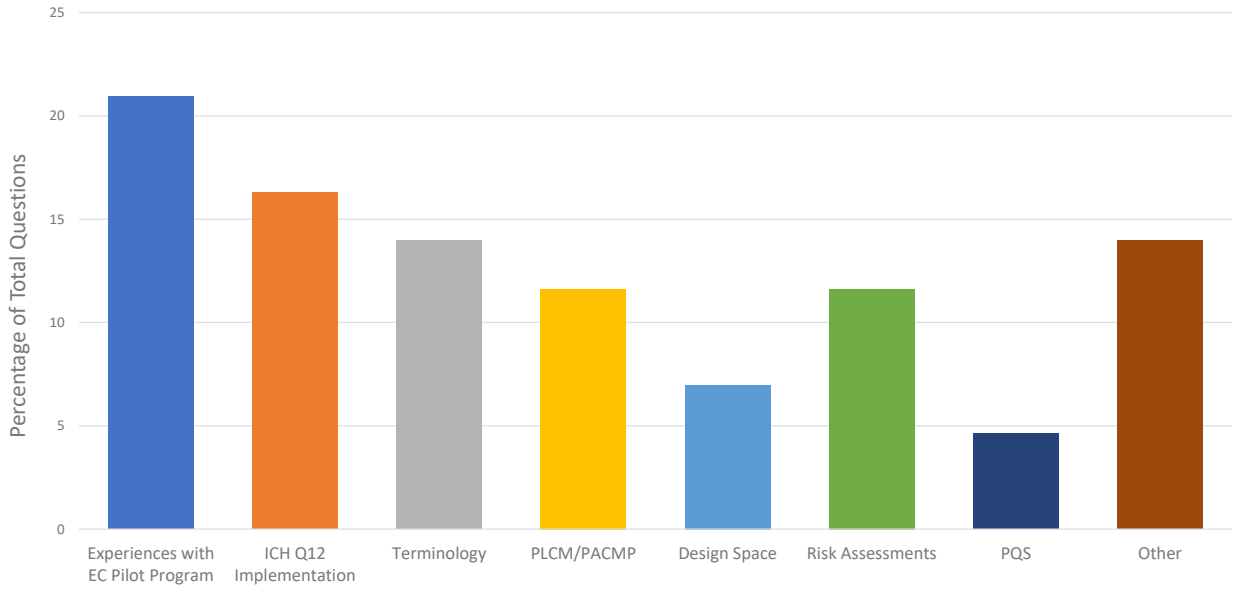
- Design space
- Experiences with the ECs pilot program
- ICH Q12 implementation
- PQS
- PLCM/PACMP
- Risk assessments
- Terminology

ISPE webinar participants were most interested in hearing about experiences with the FDA ECs Pilot Program (Figure 4). FDA perspectives on common themes and what FDA found challenging, as well as the industry perspective on the overall pilot experience, were major themes. Implementation of ICH Q12, particularly from a regulator perspective, was the next most common topic. The status of implementation at the FDA, considerations regarding a harmonized approach across health authorities, and an understanding of how to implement ICH Q12 concepts for accelerated biologics program were of interest. Overall, these themes highlight areas of opportunity for future improvements as implementation of ICH Q12 progresses.

CONCLUSIONS

As described in the case studies, many companies have formed internal teams to implement the necessary adjustments to

Figure 4: Overview of industry feedback during ISPE webinar.



systems in preparation for formal implementation of ICH Q12. Initial experience with utilization of the regulatory tools has advanced collective knowledge that will help with future submission. These tools will enable and encourage increased transparency between industry and regulators.

However, challenges still exist, as flexibility in postapproval change management has not been fully realized. In certain cases, local guidance and regulation are not yet compatible with the ICH Q12 concepts, and thus, no implementation or partial implementation will result. Lack of global convergence and alignment on implementation approaches, as well as legislative constraints, will give rise to divergent implementation strategies among health authorities. There are existing submission pathway differences and diversity in timing of approvals. Lack of alignment for data expectations regarding necessary information and level of detail in the regulatory dossier is also a challenge and will need to be addressed. Ideally, the content of the PLCM document and PACMPs should be aligned and there should be global approval of one set of ECs. Efforts to pursue global alignment of these ICH Q12 concepts will result in greater harmonization.

Worldwide adoption of ICH Q12 tools can provide a consistent approach to PLCM, with the potential for application in nonICH countries as well. As discussed, the harmonized approach to postapproval change management described in ICH Q12 will indeed "benefit patients, industry, and regulatory authorities by promoting innovation and continual improvement in the pharmaceutical sector, strengthening quality assurance and improving supply of medicinal products [1]."

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ICH QUALITY GUIDELINES:
Present Initiatives and ISPE Involvement

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In its 30-year history, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has covered a wide range of topics to generate quality, safety, efficacy, and multidisciplinary harmonized guidelines. As science advances, issued guidelines are being updated and new guidelines are proposed in a pipeline of potential future activity. This article summarizes all quality and related multidisciplinary guidelines and discusses new topics in some detail. ISPE's role in guideline development and implementation is highlighted, such as teams for commenting on draft guidelines and for assistance with guideline implementation and training.

At its inception, ICH—formerly the International Conference on Harmonisation—developed a series of indispensable technical quality guidelines, then expanded to issue some multidisciplinary guidelines (e.g., common technical document [CTD]). It further progressed to issue a groundbreaking series of guidelines on the application of science- and risk-based approaches to drug product development and manufacturing, and associated regulatory applications. In parallel, ICH expanded its membership and influence beyond the original "six pack" of regulators and industry associations from the US, Japan, and EU to 17 country regulators and global industry associations, plus 32 observers, as of 2021 (see Figure 1 [1]).

ICH was formed at a meeting in April 1990 when the regulatory agencies and industry associations of Europe, Japan, and the United States met [2]. Prior to the formation of ICH, applications for new drug products in Europe, Japan, and the US were very different, often requiring separate studies and data, with results presented in different formats and styles. These differences resulted in significant duplication of effort and many misunderstandings.

The goal of ICH was, and still is, promotion of public health through international harmonization that contributes to [3]:

- Prevention of unnecessary duplication of clinical trials and postmarket clinical evaluations
- Development and manufacturing of new medicines
- Registration and supervision of new medicines
- Reduction of unnecessary animal testing without compromising safety and effectiveness

ICH accomplishes these goals through technical guidelines that are implemented by regulatory authorities.

ICH is a unique organization: one of the factors for its success is the strong cooperation between industry organizations and regulators using a consensus-driven approach. In its first decade, ICH concentrated on a prioritized series of core regulatory studies in the areas of efficacy, quality, and safety. As ICH activity continued into the new millennium, the need to expand communication and dissemination of information on ICH guidelines with additional regions became a key focus. A significant step was taken in 2015 when ICH underwent a series of organizational changes and a name change to support extending the benefits of harmonization beyond the founding regions.

ICH members and observers, as of 2021, are listed on the ICH website (with explanations of abbreviations) and summarized in Figure 1.

There are some differences in roles and responsibilities between the various types of members and observers, but at a high level, members have voting rights, whereas observers can comment but not vote. ICH guidelines are approved by regulatory members in step 4 of the ICH process (Figure 2).

Figure 1: ICH Current Members and Observers.

MEMBERS

Founding Regulatory Members
- EC, Europe
- FDA, United States
- MHLW/PMDA, Japan

Founding Industry Members
- EFPIA
- JPMA
- PhRMA

Standing Regulatory Members
- Health Canada, Canada
- Swissmedic, Switzerland

Regulatory Members
- ANVISA, Brazil
- HSA, Singapore
- MFDS, Republic of Korea
- NMPA, China
- TFDA, Chinese Taipei
- TITCK, Turkey

Industry Members
- BIO
- Global Self-Care Federation
- IGBA

OBSERVERS

Standing Observers
- IFPMA
- WHO

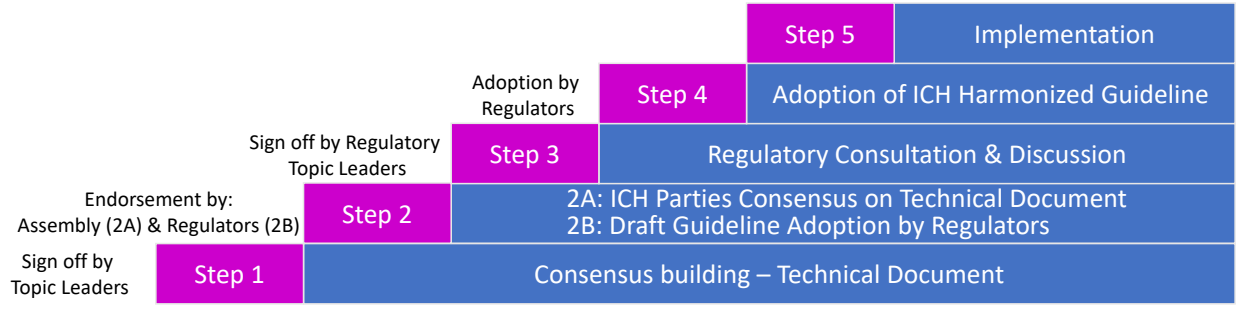
Legislative or Administrative Authorities
- ANMAT, Argentina
- CDSCO, India
- CECMED, Cuba
- COFEPRIS, Mexico
- CPED, Israel
- INVIMA, Colombia
- JFDA, Jordan
- MMDA, Moldova
- MOPH, Lebanon
- National Center, Kazakhstan
- NPRA, Malaysia
- NRA, Iran
- Roszdravnadzor, Russia
- SAHPRA, South Africa
- SCDMTE, Armenia
- SFDA, Saudi Arabia
- TGA, Australia

Regional Harmonisation Initiatives (RHIs)
- APEC
- ASEAN
- EAC
- GHC
- PANDRH
- SADC

International Pharmaceutical Industry Organisation
- APIC

International Organisation regulated or affected by ICH Guideline(s)
- Bill & Melinda Gates Foundation
- CIOMS
- EDQM
- IPEC
- PIC/S
- USP

Figure 2: Steps in the ICH process for guideline development [4].



In short, ICH has expanded its global reach and influence to encompass well over half of the world's population. Its work products are required to be implemented by regulatory members; however, the concepts and ideas are often considered by nonICH members as well within their regulatory frameworks.

ICH GUIDELINE PROCESS

The process for producing an ICH guideline [4] is summarized in Figure 2. The main steps for members of industry not involved in the ICH process are in step 3, when a draft consensus guideline is agreed upon. Each ICH regulatory agency circulates this draft guideline for comment using its local procedures and comments can be made according to the local regulatory process, usually, but not inclusively, via an industry association. Comments can also be made by interested individuals outside the ICH-affiliated regions, usually via an industry association.

ISPE ACTIVITY

For quality topics considered of interest to ISPE members, an ISPE formal commenting process [5] is used, which is managed by ISPE's

Table 1: Summary of ICH-approved quality guidelines.

ICH Guideline Reference	Topic and Series Title	Subtopic Title or Topic Description
Q1	Stability	A. Stability Testing of New Drug Substances and Products B. Stability Testing: Photostability Testing of New Drug Substances and Products C. Stability Testing for New Dosage Forms D. Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products E. Evaluation of Stability Data F. (Stability Data Package for Registration Applications in Climatic Zones III and IV – withdrawn)
Q2	Analytical Validation	Validation of Analytical Procedures: Text and Methodology
Q3	Impurities	A. Impurities in New Drug Substances B. Impurities in New Drug Products C. Maintenance of the Guideline for Residual Solvents D. Guideline for Elemental Impurities E. Impurity: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics
Q4	Pharmacopoeias	A. Pharmacopoeial Harmonisation B. Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions C. Annexes for individual monographs – see ICH website
Q5	Quality of Biotechnological Products	A. Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin B. Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products C. Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products D. Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products E. Comparability of Biotechnological/ Biological Products Subject to Changes in Their Manufacturing Process
Q6	Specifications	A. Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances B. Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
Q7 Q7 Q&As	Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients	This document is intended to provide guidance regarding Good Manufacturing Practice (GMP) for the manufacturing of Active Pharmaceutical Ingredients (APIs) under an appropriate system for managing quality.
Q8 Q8/9/10 Q&As Q8/9/10 Implementation	Pharmaceutical Development	To describe the suggested contents for the 3.2.P.2 (Pharmaceutical Development) section of a regulatory submission. The Pharmaceutical Development section should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use.
Q9	Quality Risk Management	To provide principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.
Q10	Pharmaceutical Quality System	To describe one comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organisation (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q8 and ICH Q9.
Q11 Q11 Q&As	Development and Manufacture of Drug Substances	Chemical Entities and Biotechnological/Biological Entities To describe approaches to developing and understanding the manufacturing process of the drug substance, and also provide guidance on what information should be provided in the dossier.
Q12	Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management	To provide a framework to facilitate the management of postapproval chemistry, manufacturing, and control (CMC) changes in a more predictable and efficient manner.

Regulatory Quality Harmonization Committee (RQHC). ISPE comments are linked to one of the regional regulatory consultation processes at ICH step 3 (see Figure 2).

In short, ICH has expanded its global reach and influence to encompass over half of the world's population. Its work products are required to be implemented by regulatory members; however, the concepts and ideas are often also considered by nonICH members within their regulatory frameworks.

APPROVED QUALITY GUIDELINES

In the first decade, ICH teams worked on quality topics described in ICH Q1–Q6, working from a prioritized list (as given on the ICH website [6] and summarized in Table 1) and focusing on applications for new drug products and substances. Quality guidelines Q1–Q6 are very technical and they impact the design of development studies and the interpretation of results for summarizing in regulatory applications. These studies generate data that are

accepted in most regions of the world, with the need for few additional region-specific requirements. The most significant studies not covered by ICH guidelines are stability studies to support hot and dry (Zone III) and hot and humid (Zone IV) regions of the world —regions that were not included under the ICH founding regulatory members. (ICH Q1F was withdrawn: ICH leaves the definition of storage conditions in Climatic Zones III and IV to the respective regions and the World Health Organization (WHO) [6].)

Following these initial guidelines, the Q7 guideline on Good Manufacturing Practice (GMP) for APIs was required because, at that time, there was increasing regulatory attention being given to GMP for APIs but no region had an API GMP guideline yet.

Due to advances in science and improved understanding, many of these guidelines have been updated; revised and continued modernization of these decades-old guidelines is expected to continue.

The guidelines are available on the ICH website, and the implemented versions are available on local regional websites. On the ICH website, references are given under each guideline to the implementation status in each regulatory region.

At the start of the new millennium, the ICH Quality Working Group developed a vision for quality:

> *Develop a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science.*

This vision drove development of a series of more conceptual guidelines, including Q8 (R2), Q9, Q10, and Q11, which introduced an enhanced science- and risk-based approach to drug development and regulatory applications.

Q8 describes how an applicant can choose to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options, and process parameters. This enhanced approach should lead to greater understanding of the product and its manufacturing process and this greater understanding "can create a basis for more flexible regulatory approaches" [7].

Q9 describes a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product life cycle. Application of quality risk management is fundamental to the enhanced approach discussed in Q8 (R2) and is also a key enabler in operation of a pharmaceutical quality system described in Q10 [8].

Q10 describes a comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organization (ISO) quality concepts, includes applicable GMP regulations, and complements ICH Q8 and Q9. ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product life cycle [9].

Annex 1 of ICH Q10, Pharmaceutical Quality System, discusses potential opportunities that could result from an enhanced regulatory approach such as "increase use of risk based approaches for regulatory inspections" and "optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement."

Due to advances in science and improved understanding, many of these guidelines have been updated; revised and continued modernization of these decades-old guidelines is expected to continue.

The concepts behind Q8, Q9, and Q10 were, in many ways, paradigm-changing and their implementation was sometimes unclear for both industry and regulators. ICH working groups strove to provide additional clarification and examples through a series of Question and Answer and Points to Consider documents.

The science- and risk-based approaches developed for ICH Q8, Q9, and Q10 were further applied to drug substances in ICH Q11, which, in its core guideline and Q&A document, also discusses some unique aspects of drug substance manufacturing such as designation of regulatory starting materials and impurity clearance.

ADDITIONAL LIFE-CYCLE GUIDANCE

Nearly a decade after implementation of ICH Q8 (R2), Q9, Q10, and Q11, it was recognized that these guidelines alone were not sufficient to deliver on the ICH vision of a harmonized pharmaceutical quality system applicable across the life cycle of the product. As discussed in the Q12 Concept Paper [10]:

> *There is a lack of a harmonised approach on technical and regulatory considerations for lifecycle management. While the concepts in ICH Q8, Q9, Q10 and Q11 provide opportunities for a more science and risk-based approach for assessing changes across the lifecycle, several gaps exist which limit full realisation of intended benefits. The envisioned post-approval 'operational flexibility' has not been achieved. The main emphasis at ICH to date has focused on early stages of the product lifecycle (i.e., development through launch).*
>
> *A similar focus is now needed for the commercial manufacturing phase in order to fill the gaps in the implementation and fully realize the opportunities promised by ICH Q8 to Q11. For*

Table 2: Summary of concepts in ICH Q12.

Concept	Objective
Established conditions (ECs)	To provide a clear understanding between the marketing authorization holder (MAH) and regulatory authorities regarding the elements to assure product quality and that involve a regulatory communication, if changed
Postapproval change management protocol (PACMP)	Regulatory tool that provides predictability regarding the information required to support a chemistry, manufacturing, and control (CMC) change and the type of regulatory submission based on prior agreement between the MAH and regulatory authority

Product life-cycle management (PLCM) document	• Serves as a central repository for:
	  • ECs
	  • Reporting category for making changes to approved ECs
	  • PACMPs (when proposed)
	  • Any postapproval CMC commitments
	• Encourages prospective life cycle management planning by MAH
	• Facilitates regulatory assessment and inspection
	• Intended to enable transparency and facilitate continual improvement

example, lack of alignment has led to confusion on the necessary information and level of detail in the dossier and its impact on change management and regulatory reporting. The lack of harmonised approaches for technical and regulatory aspects for lifecycle management can hinder innovation and continual improvement in the pharmaceutical and biotechnology sectors.

Consequently, ICH initiated the development of ICH Q12, "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management," which was adopted in November 2019 [11].

Q12 has introduced new regulatory tools and enablers, some of which already existed in some ICH regions; however, these were not optimally applied by sponsors and accepted or understood in other regions. Examples of such tools and enablers are:

- Established conditions (ECs)
- Postapproval change management protocol (PACMP)
- Product life cycle management (PLCM) document

A summary of these concepts is given in Table 2.

Although finalized in November 2019, as of spring 2021, ICH Q12 is not yet fully implemented in any region, which is not unexpected given that the current regional legislation may not easily allow implementation of all concepts introduced in ICH Q12. An ICH Q12 Implementation Working Group continues to work on developing training material.

Figure 3: Submission and review process.

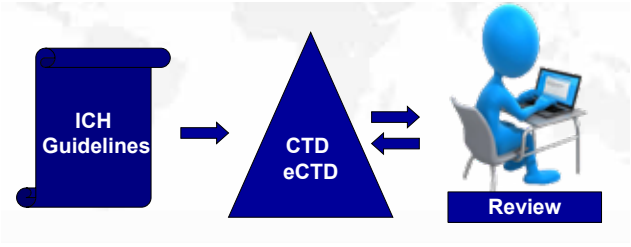
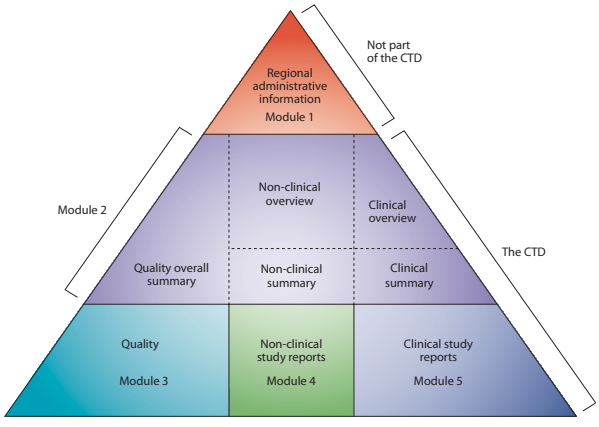


Figure 4: CTD triangle.



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

CTD and Electronic CTD

In parallel with ICH quality topics Q1–Q6, the multidisciplinary topic (M4) delivered the common technical document (CTD), which is considered a major success for ICH. Also, in parallel, a team of specialists issued standards to support electronic submission of a CTD (eCTD). An overview of the regulatory submission and review process is given in Figure 3.

CTD brings together all quality, safety, and efficacy information in a common, harmonized format, accepted by regulators in all ICH regions. It has revolutionized regulatory review processes for regulators and industry. The structure of a new drug product application and the relationship to the quality, safety, and clinical topics of CTD are shown in Figure 4.

The agreement to assemble all quality, safety, and efficacy information in a common format has led to harmonized electronic submission that, in turn, has facilitated convergence of review practices. For industry, it has reduced the need to reformat the information for submission to the different ICH regulatory authorities. It also enabled some cross-region initiatives: for example, the EMA-FDA Quality by Design (QbD) pilot program [12]. The aim of this pilot program was to facilitate the consistent implementation of QbD concepts introduced through ICH Q8, Q9, and Q10

Table 3: ICH quality and multidisciplinary guidelines issued since 2003.

ICH Guideline Reference	Topic Title	Objective
M7	Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk	To provide a practical framework that is applicable to the identification, categorization, qualification, and control of DNA reactive (mutagenic) impurities to limit potential carcinogenic risk.
M9	Biopharmaceutics Classification System-based Biowaivers	To provide recommendations to support the biopharmaceutics classification of drug substances and the biopharmaceutical classification system (BCS)-based biowaiver of bioequivalence studies for drug products.

documents and to harmonize regulatory decisions to the greatest extent possible across the two regions.

There remain, however, some region-specific quality requirements in terms of content and presentation for new applications—for example: in Japan, the Quality Overall Summary is of a different level of content because it is the primary review document. Some challenges remain for the quality topics; for example, the content of submissions for postapproval submissions can differ across regions. Some of these challenges are being addressed as part of some ICH current initiatives.

MULTIDISCIPLINARY GUIDELINES

Approved relevant multidisciplinary topic guidelines applicable to CMC development and registration of new drug products are summarized in Table 3.

M7 is intended to resolve inconsistencies in the early guidances between the EMA and FDA relating to impurities that are DNA reactive, and the recommendations in the ICH general impurities guidance, Q3A. A science- and risk-based approach is used in establishing levels of mutagenic impurities that are expected to pose negligible carcinogenic risk.

The BCS-based biowaiver described in M9 is only applicable to immediate-release, solid, orally administered dosage forms or suspensions designed to deliver drug to the systemic circulation; drug products with narrow therapeutic index are excluded from eligibility. This guidance is useful to support potential drug product changes during clinical development and through to commercialization.

ICH QUALITY AND MULTIDISCIPLINARY INITIATIVES

Current activity is driven by new technology and scientific advancement and has led to revision of some signed off guidelines, as well as new topics. A major milestone for an ICH guideline is the issuance of a draft consensus document at step 2. Current ICH guidelines that are pre-step 2 are summarized in Table 4.

Table 4: Current ICH quality and multidisciplinary activities prior to draft guideline.

ICH Guideline Reference	Topic	Objective	Status
Q3E	Impurity: Assessment and Control of Extractables and Leachables (E&L) for Pharmaceuticals and Biologics	To develop internationally harmonized guidance on E&L assessment and control required based on science- and risk-based principles.	Draft document for consultation due in November 2022
Q5A(R2)	Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin	To address new biotechnology product types, advances in manufacturing technology, analytical methods for virus testing, and scientific knowledge that have occurred since publication of the original document.	Draft document for consultation due in November 2021
Q9 (R1)	Quality Risk Management	To make limited and specific adjustments to specific chapters and annexes of the current ICH Q9 Guideline on Quality Risk Management (QRM); To develop specific training materials (with examples) to supplement the existing ICH briefing pack on ICH Q9, as well as to explain and facilitate the implementation and application of the proposed revisions.	Working Group commenced in January 2021
Q13	Continuous Manufacturing (CM) of Drug Substances and Drug Products	To define regulatory expectations for development, implementation, and assessment of CM (small and large molecule drug substances and drug products).	Draft document for consultation due in Q3 2021
Q14/Q2(R2)	Analytical Procedure Development and Revision of Q2 (R1) Analytical Validation	Q14 will focus on information on development of methods to support use of real-time release methods and provide a basis for flexible regulatory approaches to analytical postapproval changes. Q2(R1) introduces validation of spectroscopic and multivariate methods.	Draft document for consultation due in Q3 2021
M13	Bioequivalence for Immediate-Release Solid Oral Dosage Forms	To harmonize bioequivalence study design and standards, which is expected would benefit both innovator and generic product development.	Draft document for consultation due in Q3 2022

Table 5: Current ICH quality and multidisciplinary activities post draft guideline.

ICH Guideline Reference	Topic	Objective	Status
M7(R2)	Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk	To incorporate acceptable limits for acceptable intakes ([AIs] or permitted daily exposures [PDEs]) for new DNA reactive (mutagenic) impurities and revising acceptable limits for impurities.	Sign off of final guideline due Q3 2021
Q3C(R8)	Maintenance of the Guideline for Residual Solvents	To maintain PDE levels for 2-methyltetrahydrofuran, cyclopentylmethylether, and tert-butanol.	Final guideline issued April 2021
Q3D(R2)	Revision of Q3D(R1) for cutaneous and transdermal products	To develop an acceptable level for elemental impurities for administration by cutaneous and transdermal routes and update PDEs for gold, silver, and nickel.	Final guideline due in Q3 2021

The existing guidelines in Table 5 have reached step 2 and issued the draft consensus guideline; they are undergoing revision based on comments received from regulatory review before final regulatory sign off and subsequent implementation.

ISPE INITIATIVES SUPPORTING ICH

To assist industry with the understanding and implementation of ICH guidelines Q8, Q9, Q10, and Q11, ISPE established the Product Quality Lifecycle Implementation (PQLI®)initiative focused on providing practical implementation guidance. Key outputs for members are the PQLI Guide series in four parts:

- Part 1, *Product Realization Using QbD: Concepts & Principles* [13]
  - Overview
  - Criticality
  - Design Space
  - Control Strategy
- Part 2, *Product Realization Using QbD: Illustrative Example* [14]
  - Drug product and API
- Part 3, *Change Management System as a Key Element of a Pharmaceutical Quality System* [15]
- Part 4, *Process Performance & Product Quality Monitoring System* [16]

Many emerging topics and other ICH topics have a related active subteam in ISPE, either through PQLI or other regulatory teams. These teams work to help develop the concepts underlying the regulatory guidances and to assist regulators and ISPE industry members with implementation.

- A knowledge management ISPE Good Practice Guide, aligned with the principles of ICH Q9 and Q10, was published in May 2021 [17]. ISPE teams have also provided training to regulators on ICH concepts to US FDA, UK MHRA, and Brazil ANVISA.

ISPE's global RQHC has established a team to assist members with implementation of revisions to Q9. The quality risk management topic is important to many ISPE programs, for example, the Drug Shortages Initiative. ISPE has provided the ICH Q9 EWG with relevant ISPE training material and PQLI documents for consideration in their deliberations.

A PQLI Continuous Manufacturing team has been established for several years. It has published multiple articles [18], sponsored biannual ISPE Continuous Manufacturing Workshops since 2016, and frequently provides sessions at ISPE conferences. It continues to track progress of the ICH Q13 guideline in preparation and is expected to comment on the ICH Q13 Step 2 draft document.

A PQLI Q12 team has been established to assist industry and regulators with implementation of ICH Q12. It is very active and published an article [18] in *Pharmaceutical Engineering*® in May-June 2019 on the challenges the ICH EWG faced in reaching consensus for the signed off ICH Q12 document. The team delivered a webinar [20] with FDA participation in March 2021 on the challenges and successes of Q12 implementation. It has provided case study examples for consideration by the ICH EWG in their efforts to produce a step 2 draft document.

Additional workgroups will continue to be added to ISPE's regulatory teams as new topics emerge.

ISPE Initiatives Supporting Future ICH Activity

ISPE has ongoing projects and initiatives that could support any future ICH activity:

- PQLI has a team working on Patient Centric Quality Standards, which hosted a session at the 2018 ISPE Quality Manufacturing Conference [21] and published an article [22]. This team is available to work on any proposed Q6A and Q6B revision.
- PQLI's Accelerated Development team has published three articles [23–25] that can help provide foundation for future related ICH topics.
- ISPE's RQHC North America Regional Focus Group has established a Modernization of Module 3 team to consider the implications for industry members on the FDA Knowledge-aided Assessment and Structured Application (KASA) and regulatory submission-associated projects. This team could support revisions to ICH M4Q CTD.
- ISPE's global RQHC has established a team to examine how the learnings from "distant assessments" and mutual reliance could be promoted and implemented in a harmonized manner based on learnings from the COVID-19 pandemic. This activity could be available to any ICH activity resulting from the ICH collaboration with PIC/S.
- ISPE has established a new ATMP Community of Practice with the goal of considering:
  - Manufacturing processes/techniques, including the development of a robust control framework to ensure

product quality
- Robust analytical and stability methodologies
- Strategies for raw materials, in process, and accelerated product release
- Regulatory landscape

FUTURE ICH ACTIVITY

In May 2020, the ICH Assembly endorsed the proposal "Revision of M4Q(R1) CTD on Quality guidance," with an M4Q(R2) informal Working Group to be established with a delayed start once the Q13 EWG would reach steps 1 and 2a/b. The Assembly supported work on the following topics:

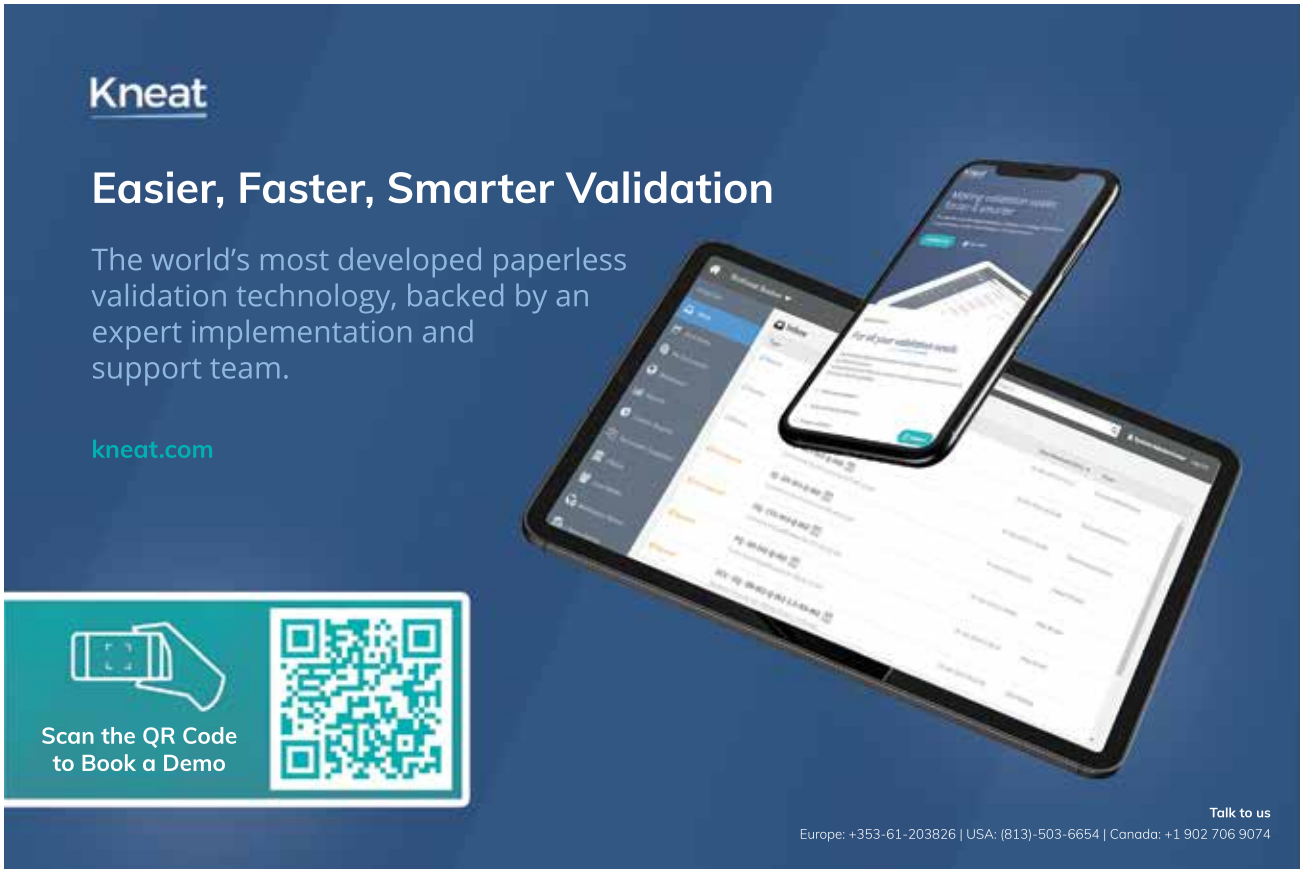
- Revision of M4Q(R1) CTD
- Structured product quality submissions

Much of this future work for the M4Q revision is driven by the US FDA and their programs on Knowledge-aided Assessment & Structured Application (KASA) [26] and Product Quality/CMC (PQ-CMC) structured product data. The vision is for a unified system that will capture and manage knowledge during the life cycle of a drug product, with consistent rules and algorithms for risk assessment, control, and communication. Such a system will facilitate computer-aided analyses of applications using structured assessment that minimizes text-based narrative. Of course, activity by the FDA has the potential to impact CTD submissions and review in all ICH regions.

There are ongoing discussions by an ICH team called the Quality Discussion Group to review new quality topics in consideration for future ICH development. A publicly available report with recommendations from this team is expected by the end of 2021. Potential recommendations are likely to include:

- Q6A and B revision
- Stability topics: Q1 series plus Q5C
- Impact of learnings from the COVID-19 pandemic, e.g., accelerated approvals
- Advanced therapy medicinal products such as gene therapy medicines, somatic-cell therapy medicines, and tissue-engineered medicines

There are other ongoing ICH activities that can influence pharmaceutical development and manufacturing. The Pharmaceutical Discussion Group (PDG) is piloting an approach for the engagement of the pharmacopoeias of the countries/regions of non-founding ICH regulatory members. The aim is to review how a selected



number of pharmacopoeial monographs considered interchangeable by European Pharmacopoeia, Japanese Pharmacopoeia, and United States Pharmacopeial Convention in Q4B Annexes could also be considered interchangeable in other ICH regulatory regions' pharmacopoeias.

ICH has agreed to a pilot collaboration with PIC/S on ICH Guideline work with relevance to both regulator assessor and inspector disciplines that may be able to build on the success of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) in mutual recognition of inspections and harmonization of GMP requirements.

The ICH Management Committee has a responsibility in the 2021 Work Plan to continue ICH-driven mechanisms to assess implementation and adherence to the ICH guidelines through surveying and results analysis.

CONCLUSION

ICH has been a successful organization for over 30 years, delivering on its mission to achieve greater harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner. Apart from the many efficacy, quality, safety, and multidisciplinary guidelines that have been issued, its success can be measured by both the increased participation and the growing number of regulatory authorities and other organizations becoming members of ICH or following its activities closely.

ISPE is an affected organization and consequently has increased its involvement: for example, by assisting with implementation and training of some quality guidelines. ISPE has positioned itself to continue assisting ICH and other harmonization processes to facilitate regulatory harmonization and mutual reliance of regulatory review and inspection to assure efficient global availability of quality medicines for patients.

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DISTANT ASSESSMENTS, AUDITS, AND REGULATORY GUIDANCE

By Christopher J. Potter and Robert W. Tribe

The ISPE Global Pharmaceutical Regulatory Summit, held virtually on 28 April 2021, brought together 11 regulators from different parts of the world to discuss how their approaches to GMP inspections have adapted to the COVID-19 pandemic.

The large number of regulatory agencies participating in a single ISPE forum is unprecedented. The regulators participating in the Summit were:

- David Churchward, Deputy Unit Manager, Inspectorate Strategy & Innovation, Medicines & Healthcare products Regulatory Agency (MHRA), United Kingdom
- Alonza Cruse, Director, Office of Pharmaceutical Quality, US FDA/Office of Regulatory Affairs (ORA), US
- Brendan Cuddy, Lead Scientific Officer, European Medicines Agency (EMA), European Union
- Marisa Delbò, AIFA Consultant, former Head of GMP API Inspections and Manufacturing Authorization Office, Italian Medicines Agency (AIFA), Italy
- Klaus Eichmueller, Darmstadt Regional Council Regierungspräsidium, Darmstadt, Germany
- Joey Gouws, Team Lead, Inspection Services, Prequalification Team, World Health Organization (WHO)
- Anne Hayes, Inspection Manager, Compliance Health Products Regulatory Authority (HPRA), Ireland and Chair of Pharmaceutical Inspection Co-operation Scheme (PIC/S)
- Manuel Ibarra Lorente, Head of Pharmaceutical Inspection and Enforcement, Spanish Agency for Medicines and Health Products (AEMPS), Spain
- Jacques Morenas, Technical Adviser of the Inspection Division Director, National Agency for the Safety of Medicines and Health Products (ANSM), France
- Carmelo Rosa, Director, Division of Drug Quality, US FDA Office of Compliance/Office of Manufacturing Quality, US
- Vladislav Shestakov, Deputy Head, State Institute of Drugs and Good Practices, Russia

A panel discussion involving the regulators was preceded by keynote presentations giving an update on the current approaches used by US FDA, EMA, MHRA, and PIC/S for remote/distant inspections.

KEYNOTES

US FDA

In his keynote presentation, Cruse said that although on-site inspections remained the "gold standard," the pandemic had forced FDA to rethink its approach to inspections by using a risk-based approach involving various oversight tools, including remote assessment of records, information sharing with trusted regulatory partners, reviewing compliance history of manufacturing facilities, analytical testing, and remote interactive evaluation (RIE) of facilities by video/live streaming of operations. Guidance for RIE was introduced in April 2021[1]. FDA used the term "Remote Interactive Evaluation" to distinguish a remote evaluation from an on-site inspection.

Cruse said that the RIE would be hosted by FDA using an FDA version of MS Teams, Zoom, or Adobe as the IT platform. A written list of observations would follow the remote evaluation, but FDA would not issue Forms 482, Notice of Inspections and Forms 483, Inspectional Observations.

Cruse said that once the pandemic was over, FDA would go back to on-site inspections but would likely use a hybrid approach by considering at least a RIE component and remote inspection of records.

FDA may use remote evaluation outcomes to decide on the acceptability of a facility for a pending application, to determine a future cGMP surveillance inspection timing and scope, and to

help resolve a "for cause" need to inspect. FDA will not use remote evaluation in lieu of an inspection.

Looking ahead, FDA will continue to leverage and maximize every available tool including operationalizing RIE. Relationships with capable regulatory partners will be enhanced.

EMA

In his presentation, Cuddy said that the pandemic had created a challenge to GMP inspectors who needed to ensure ongoing verification of GMP compliance was being maintained. EMA recognized the need for regulatory flexibility until the end of the pandemic, using approaches such as automatic extension of the validity dates for GMP certificates and product-specific GMP flexibility for crucial medicines and process validation.

Cuddy said that a distant assessment guidance document to directly verify GMP compliance had been developed and published in October 2020 by EMA [2]. This guidance document defined "distant assessment" as well as guidance for the planning, preparation, conduct, and post-assessment phases of the distant assessment.

Cuddy said distant assessments have broad application and can be performed for all types of sites, dosage forms, and preapproval inspections. They can result in the granting of GMP certificates, but with the certificate indicating that the determination was based on a remote assessment. He emphasized that a distant assessment does not replace an on-site inspection, which should be conducted when circumstances permit. He said that if a distant assessment does not permit the granting of a GMP certificate, a clock-stop would be triggered until an on-site inspection was possible.

For new sites or for pre-approval inspections, Cuddy said if any critical deficiencies were identified, the relevant application would be paused until an on-site inspection could be performed. For other types of distant assessments, if any critical deficiencies were identified, a statement of non-compliance may be issued.

Cuddy concluded by saying that distant assessment has proven to be a useful tool in the supervisory toolbox . He said good positive feedback had been received from inspectors and inspected companies on the conduct and results of distant assessments to date. Distant assessments provide an additional control measure to verify compliance. The future will see more international authority use of distant assessment, but distant assessment will not replace on-site inspection.

MHRA

Churchward discussed current and future challenges arising from the pandemic. Current challenges include severe travel restrictions, global supply pressures, and the backlog of GMP inspections. Future challenges when the pandemic is over would likely include the development of regulatory approaches to a digital environment and the harmonization of remote assessments between regulators to create an environment of reliance.

Churchward asked whether the regulatory changes arising from the pandemic are here to stay, including remote assessments.

Looking ahead, FDA will continue to leverage and maximize every available tool including operationalizing RIE. Relationships with capable regulatory partners will be enhanced.

It was his belief that because a distant assessment was a rapid and flexible monitoring tool, it would continue to be used after the pandemic, but in a hybrid form, particularly for low-risk situations. He stressed that collaboration between regulatory agencies had been very good during the pandemic, and he advocated for this to continue and increase with opportunities taken to harmonize approaches and potentially regulations for distant assessments leading to more reliance between agencies. He mentioned that PIC/S has a key role in facilitating future closer cooperation and mutual reliance.

PIC/S

PIC/S is an informal cooperative scheme that had been operating for 50 years, comprising 54 member authorities from all over the world (including countries in Europe, Africa, the Americas, Asia, and Australasia). Membership in PIC/S enables member authorities to share information of GMP-related topics, including GMP inspection reports. The mission for PIC/S is "To lead the international development, implementation and maintenance of harmonized GMP standards and quality systems of inspectorates in the field of medicinal products." [3]

Hayes said that PIC/S held a training seminar for inspectors each year, with the most recent seminar in December 2020 covering the topic of distant assessment. This seminar revealed that because the terminology used for on-site assessments varied among member authorities, there was a need for harmonization of terminology.

Hayes said that seminar participants indicated their strong support for the development of guidelines and tools to harmonize procedures for distant inspections in order to facilitate continued reliance between international regulatory partners. She said that PIC/S had formed a working group to commence work on the preparation of these guidelines, tools, and training.

PANEL DISCUSSION

A two-hour panel discussion with all the regulators followed, moderated jointly by Thomas Hartman, ISPE President and CEO, and Thomas Zimmer, ISPE Vice President, European Operations.

Here is a summary of main points from the panel discussion.

Criteria for Distant Assessments

In response to a question regarding criteria for choosing different approaches, all panelists agreed that a risk-based approach was taken. Cruse said that because of the COVID-19 health emergency, FDA limited unnecessary face-to-face contact by conducting prioritized domestic on-site inspections only for those situations that were deemed "mission critical," which included manufacturers of breakthrough therapies, unmet medical needs, etc. The term "mission critical" was defined in an FDA Guidance document covering Q&As [4].

Cuddy said that EMA confers with the relevant supervisory authority and the rapporteurs for the product concerned to decide on the need for an on-site inspection, with the criticality of the product also taken into account.

Gouws said that each regulatory authority has their own procedures to determine when to carry out on-site inspections. She said that WHO had developed a guidance document on conducting pre-qualification inspections remotely [5].

Preparation and Performing

All panelists said that as with on-site inspections, the key elements for distant assessments were transparency, integrity of data, complete and accurate data, truthfulness, and ease of access to subject matter experts (SMEs). Cruse said that there was evidence that some companies were selective with the information they shared; e.g., not all OOS data was shared, resulting in FDA needing to probe deeper and to ask repeatedly for information.

Eichmueller, Delbò, Morenas, and Lorente agreed that although hybrid inspections were being done in Europe, the German, Italian, French, and Spanish health authorities always preferred to do on-site inspections. Distant assessments do not provide sufficient assurance of compliance and take more resource for preparation and conducting, they said. It was considered that anything done remotely was simply an assessment and not an inspection. On-site inspections were necessary for critical products.

Morenas said that it was necessary to establish how to manage and protect the flow of information received during distant assessments. Cuddy confirmed that cybersecurity is not a new topic; both sides, agencies and industry, need to invest in security to help prevent cyberattacks.

Gouws said that it was important for WHO to know which other regulatory authorities are planning to carry out a distant assessment of specific manufacturing sites so that WHO can request a joint distant assessment. She said that this approach was appreciated by industry. She also said that industry can help to facilitate distant assessments by sharing data well in advance of the distant assessment, having suitable translators available, and having the company representative supported by suitable numbers of company staff in the war room, including plentiful technical SMEs.

Outcomes

Churchward said that as legislation in the UK did not dictate that GMP inspections must be on-site, MHRA can use other methods to determine GMP compliance. He added that where MHRA had seen enough information to give confidence of GMP compliance, a GMP certificate would be issued, but this certificate would bear a note to indicate that it was based on a remote assessment. Other EU agencies also confirmed that GMP certificates were being issued based on distant assessments, but that a suitable annotation was included.

Shestakov said that the Russian regulatory authority had never stopped issuing GMP certificates during the pandemic. He said that in order to avoid drug shortages in Russia, legislative changes had been made to enable remote assessments to be carried out, and GMP certificates could be issued following such assessments.

Technology

Hayes said that the pharmaceutical industry in Ireland had indicated to HPRA its strong support for distant assessments. She confirmed that distant assessments required a significant amount of preparation by regulatory authorities and because of this, it was advisable for companies to conduct a review of their IT capabilities, including digital tools and bandwidth because a regulatory authority cannot do a remote assessment if a site is unable to do video streaming effectively.

Shestakov said that from April 2020, the Russian regulatory authority had conducted 300 remote assessments, with some of the sites found not ready to receive the remote assessment because the inspectors could not get to the deepest manufacturing areas. He said that companies need to build the infrastructure to receive the remote assessment, including suitable video cameras; also, inspectors and manufacturing staff need suitable training about remote assessments.

To conduct remote inspections, it is imperative that some technical requirements are met, e.g., to ensure a secure communication channel by using private virtual networks. Keys and/or coded streaming of video and audio information should be shared in advance, preferably with the use of secure real-time transport protocol (SRTP). When it comes to using smartphones, there are prescribed requirements for smartphone's camera and protection class. In addition, it is preferable that smartphones have a portable tripod or other anchorage that ensures simultaneous use of smartphones and backlighting lamps. Availability of a portable spare battery is important.

Comparing On-site and Distant Assessments

With regard to potential differences between on-site inspections and distant assessments, Churchward said that MHRA had done an analysis to see if there was any difference in the number and type of deficiencies found. He said that this study had found no significant differences; this included quality system and facility failures, which

trended much the same. Also, for hybrid inspections there were no significant differences.

In contrast, Eichmueller said that the German regulatory authorities had found fewer operational deficiencies during distant assessments, which is another reason why they should not be considered comparable to on-site inspections.

Sharing Information Among Health Authorities

Rosa said that FDA had been sharing inspection information under the EU mutual recognition agreement (MRA) for some years now; this was even more important and relevant at this time of the COVID-19 pandemic. He said that the challenge was that sometimes the scope of the inspection information shared may be different than what is required by FDA. Cruse added that in addition to the EU MRA, FDA also obtains information from EU and PIC/S member authorities about inspections carried out in other countries. Cuddy said that EU was using inspection reports from other regulatory authorities, including PIC/S member authorities.

All panelists stressed the need for sharing of information through mutual reliance with PIC/S regulatory partners to support distant assessments and the relevant outcome; however, each agency was making its own decisions. Where present, MRAs are different from "information sharing" and do not extend to distant assessments.

Hayes said that PIC/S had introduced a guidance document on "Inspection Reliance" in 2018 [6], which has been instrumental in facilitating the sharing of inspection information among PIC/S member authorities at a time when on-site inspections had been significantly curtailed during the pandemic.

Terminology

Cuddy admitted that even within Europe, there was some disagreement among regulators about terminology for the terms distant, remote, and desktop inspection assessment.

Hayes said that one of the action items arising from the virtual PIC/S Committee meeting held during the previous week was to request International Coalition of Medicines Regulatory Authorities (ICMRA) to formulate a reflection paper on remote/distant assessment, which would include the harmonization of terminology, and for PIC/S to develop harmonized procedures for remote/distant assessments. She admitted that as terminology around remote/distant assessments was used in different ways by different regulatory authorities, it may be difficult for ICMRA to harmonize the terminology.

The Future of Distance Assessment

Each panelist provided their thoughts for the future about the use of distant assessments. FDA, EMA, MHRA, and 28% of respondents in a PIC/S survey believed that there was a place for distant assessments in the future, potentially using hybrid ways of working. However, all panelists agreed that a distant assessment cannot substitute for a face-to-face on-site inspection.

Regulators from France, Germany, Italy, and Spain said that the distant assessment was only an emergency tool and cannot replace a face-to-face on-site inspection. The distant assessment has many shortcomings and provides less information, and, because of this, on-site inspections should resume as soon as possible. Morenas and Eichmueller said that maybe a distant assessment could be used for low-risk situations only.

For Russia, Shestakov said that distant assessments were an interim measure only but could still be used in the future under special circumstances. He said that it was likely that the hybrid model would be used in the future. Gouws said distant assessments may be used by WHO as a tool for training in the future.

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Disclaimer

This is a brief and informal synopsis of responses from regulators during a panel dialog at an ISPE event in April 2021. It has not been vetted by any agency and does not represent official guidance or policy of any agency.

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PQLI®: ADVANCING INNOVATION AND REGULATION

By Christine M. V. Moore, PhD, Nina S. Cauchon, PhD, Gabriella M. Dahlgren, PhD, Maria L. Hoffman, Maurice B. Parlane, BTech, Roger W. Quan, PhD, Wyatt J. Roth, PhD, and Eli Zavialov, PhD

A unique aspect of the pharmaceutical industry is the pairing of innovation and regulation. For nearly two decades, ISPE's Product Quality Lifecycle Initiative (PQLI®) has worked at the nexus of pharmaceutical manufacturing technology and regulation to bring forward solutions that help advance new regulatory and technology approaches. This article summarizes the historical and current PQLI work in realizing this mission, thus supporting medicines reaching patients around the globe.

PQLI initiated in the early 2000s, concurrent with the advancement of the pharmaceutical quality by design paradigm and ICH guidelines ICH Q8 on pharmaceutical development, ICH Q9 on quality risk management, ICH Q10 on pharmaceutical quality systems, and later ICH Q11 on development and manufacture of drug substances. The early PQLI technical teams sought to clarify how practitioners can implement the new quality by design concepts in a way that would benefit both regulators and industry.

PQLI teams authored several seminal papers [1–4], culminating in PQLI Good Practice Guides [5–8] that include detailed illustrative examples. These articles and guides formed a solid foundation for quality by design and have been influential for both industry and regulators to this day.

PQLI'S PROGRESSION

ISPE and PQLI have transformed through the years to stay current with emerging technology and regulatory trends. Today's PQLI technical teams cover a broad range of topics related to new regulatory and technology approaches. A view of current and past PQLI teams reflecting their role in pharmaceutical product life cycle is depicted in Figure 1. Although the topics may be diverse, each PQLI technical team has a common mission to deliver state-of-the-art content that advances regulatory science for pharmaceutical chemistry, manufacturing, and controls (CMC).

The current PQLI teams include Continuous Manufacturing, Transportable & Point of Care Manufacturing, Patient Centric Specifications, ICH Q12 Implementation, and Process Validation.

Each PQLI team has its own life cycle. PQLI topics are identified through ISPE regulatory committees and developed through small teams of subject matter experts (SMEs) who are ISPE members. The PQLI technical teams work to understand the current landscape and to form consensus approaches for these emerging topics, identifying the relevant regulatory and technical questions and potential solutions.

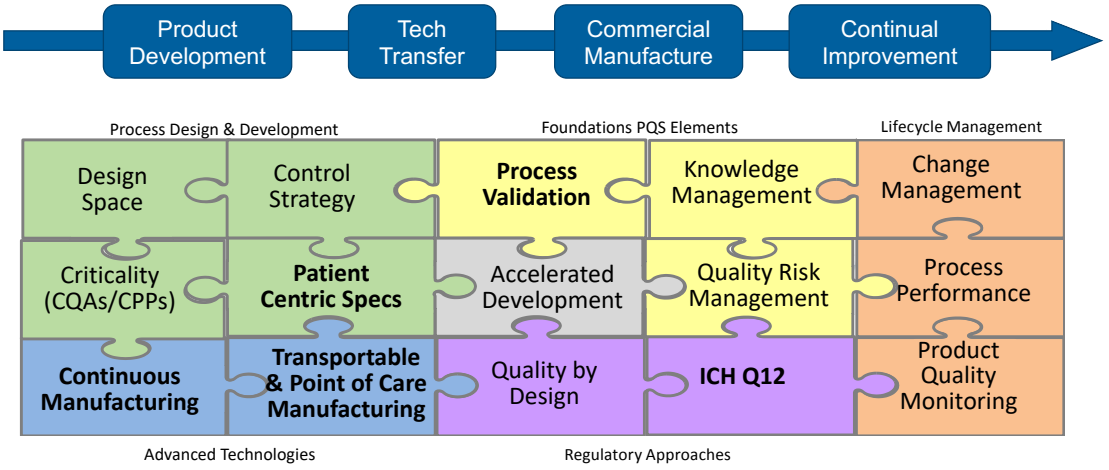
Their findings are made available through ISPE and other conferences, ISPE white papers, and *Pharmaceutical Engineering*® articles. As PQLI topics develop and fully mature, they may be "retired" from PQLI or reshaped into a format where SMEs can more broadly share their knowledge and experience, such as through an ISPE Community of Practice (CoP). Alternatively, a PQLI team can evolve into a writing team for an ISPE Good Practice Guide. One such example is the recently retired PQLI technical team on Knowledge Management, which recently published an ISPE Knowledge Management Good Practice Guide [9].

Today's technical teams in PQLI address some of the greatest current regulatory and technical challenges of pharmaceutical manufacturing as they strive to shape the regulatory landscape for the successful implementation of new technology and regulatory approaches. A brief discussion of each current PQLI topic follows.

PQLI Continuous Manufacturing Working Group

Continuous manufacturing (CM) is emerging as the new and next generation of pharmaceutical manufacturing processes. The

Figure 1: PQLI integration over the product life cycle.



technology is amenable to helping resolve current needs within our industry such as drug shortage, variable demand in production volume from issues such as a pandemic, faster transfer to manufacturing, and more local or regional manufacturing. CM is supported by other advanced technologies such as process analytical technology, modeling, real-time release testing, and continuous process verification. The draft FDA guidance on CM defines continuous manufacturing as "an integrated process that consists of a series of two or more unit operations ('the system'). In such a process, the input material(s) are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system" [10].

Implementation of CM introduces some unique challenges related to manufacturing process controls and assurance of product quality, especially for multinational companies that are trying to obtain global regulatory approvals without the benefit of harmonized regulatory guidance documents. Addressing these challenges has been and still is the focus of the CM team within PQLI.

As with any new technology, it is important that early adopters have opportunities to share their successes as well as pain points to help expand use of the technology and close gaps. The PQLI CM team has addressed these issues through biennial ISPE CM workshops. The inaugural CM workshop in 2016 focused on the business benefits and regulatory and technical challenges of the newly emerging technology [11]. This workshop led to the initiation of the PQLI CM team. In 2018, the focus was on small molecule API and drug product, which was the more mature platform for CM at that time, with multiple products having gained regulatory approvals. The workshop brought together regulators, industry members, and academics from across the globe. Building on the success of the 2018 workshop, a virtual ISPE CM Workshop was held in 2020. As a sign of the maturation and expanded use of the technology, the workshop featured two parallel tracks for small molecules and biologics.

To ensure a broader reach beyond workshops, the team has also focused on publishing papers to address novel elements of CM. Two theme issues of *Pharmaceutical Engineering*® have been published. In May-June 2019, the focus was on holistic control strategy, process validation, sampling, and regulatory progress globally [12]. The current issue [13] focuses on the progress in the past two years, highlighting the advancement of CM for biologics, the global acceptance of CM, development and validation of a CM process, and summary of the work that is being done within ISPE in support of CM equipment development.

With the progression of ICH Q13 Continuous Manufacturing of Drug Substance and Drug Products [14], there will be opportunities for the PQLI CM Working Group to comment on the draft guidance document and to generate working products to support the successful implementation of the guideline across our industry and around the world.

PQLI Transportable and Point of Care (POC) Working Group

Transportable and point of care manufacturing is the subject of the newest PQLI technical team; it is emerging as an enabler for speed to market by providing decentralized manufacturing and distribution closer to the patient. See Table 1 for different types of mobile manufacturing and the applications they support.

Process intensification creates opportunities for facilities with a smaller footprint that can be replicated cost effectively, reducing supply risk through redundancy and allowing flexibility to respond to changes in market demand. Mobile manufacturing affords the opportunity to change the regulatory pathway in a science- and risk-based manner. The potential for portable manufacturing is immense with possible manufacturing applications for small molecule, biotechnology, and cell and gene therapy products, especially if utilizing smaller equipment such as with CM. Regulatory flexibility and speed can be achieved with strong

Table 1: Types of modular, mobile, and point of care manufacturing configurations.

Manufacturing Type	Volume Supported	Applications
Portable on-demand modular cleanrooms (PODs)	Low to moderate	Clinical Commercial Lab
Manufacturing trailers	Low	Clinical Lab Some commercial
Portable skid	Low to moderate	Clinical Commercial
Suitcase manufacturing	Single dose	Clinical Commercial

collaboration between industry and regulators, as shown during the COVID-19 pandemic. The question for mobile manufacturing then becomes: can elements from this experience become part of the normal business process?

Risks to product quality for transportable manufacturing tend to be lower than traditional site changes due to the sameness or similarity of equipment and scale. Two scenarios are envisioned that avoid traditional scale-up and technology transfer issues: (a) the same transportable unit can be relocated from one location to another, and (b) the transportable unit can be replicated or cloned using the same design and equipment. However, in many regions the regulatory framework is not in place to provide benefit from the lowered risk related to transportable manufacturing. The lack of regulatory framework leads to unique challenges, especially for multinational companies that are trying to obtain global regulatory approvals without the benefit of harmonized regulatory guidance documents. Addressing these opportunities and challenges is the focus of the Transportable and POC team.

The adoption of new technology must start with a level of understanding of the benefits and challenges that exist with implementation. To that end, the team will introduce the different types of mobile manufacturing and drive an understanding of the technical, quality, and regulatory aspects of the technology at various forums.

PQLI ICH Q12 Working Group

ISPE PQLI ICH Q12 Working Group was formed in 2019 with the focus on supporting the adoption of ICH Q12 guideline on pharmaceutical product life cycle management [15] by regulatory agencies and enabling the implementation of the ICH Q12 principles by pharmaceutical and biopharmaceutical companies. ICH Q12 is a transformational guideline that has a wide scope of applicability. ICH Q12 builds on the framework laid down in ICH Q8–Q11 guidelines and has the potential to remediate key remaining technical and regulatory hurdles that prevented the full adoption and implementation of flexible science- and risk-based approaches to postapproval CMC change management.

The progress to date on implementation of ICH Q12 has been slow. ICH is currently completing the preparation of training materials and is planning the initiation of a training program in fall 2021. The EMA published a note on EU implementation of ICH Q12 in March 2020 [16], while the FDA was expected to issue its ICH Q12 implementation guidance in May 2021 [17]. Many other global health authorities such as Japan, Brazil, Canada, and China have discussed similar plans for issuing guidance for implementation of ICH Q12 in the next year or two.

Among the ISPE PQLI ICH Q12 Working Group's recent accomplishments was a feature article in ISPE's *Pharmaceutical Engineering* May-June 2020 issue that discussed key aspects of ICH Q12 and highlighted major changes from Step 2 (draft) to Step 4 (final) guideline document [18]. The working group has also played a leading role in organizing ICH Q12–focused sessions at conferences and workshops featuring a diverse group of speakers from both the biopharmaceutical industry and regulatory agencies at the 2020 ISPE Biopharmaceutical Manufacturing Conference, 2020 ISPE Annual Meeting & Expo, and 2021 FDA-Xavier PharmaLink conference. Some of the key themes that emerged from these meetings included the importance of robust criticality assessments and the effective communication of their results and data to regulators in support of proposed established conditions (ECs); a wide variety of terminology and approaches used by the applicants and the need for greater alignment in this area; and a better understanding of what constitutes a robust pharmaceutical quality system and how it should be conveyed to regulators.

Significant interest arose around key lessons learned from the recent FDA Pilot on Established Conditions and how the FDA plans to implement ECs and product life cycle management (PLCM) documentation in the future. Some of these questions and concerns have been addressed in the recently published FDA draft guidance on ICH Q12 implementation [17].

Going forward, the working group plans to continue its efforts to drive global ICH Q12 adoption, define key opportunities and challenges with Q12 implementation, and develop examples and trainings that help improve the understanding of the key guideline principles. ICH Q12 is a complex guideline with novel tools and approaches, some of which are currently not fully compatible with the existing legal frameworks in certain markets. Therefore, for the full potential of ICH Q12 to be realized, it is critical to foster a robust global dialogue around current implementation challenges and to share the best implementation practices. To achieve its ambitious mission, the working group seeks to expand its partnerships with other cross-industry groups, including those under ISPE PQLI initiative, as well as ICH and other global regulatory bodies.

PQLI Patient Centric Specifications Working Group

Patient-centric specifications are those focused on delivering a quality product based on patient needs. Historically, regulatory agencies evaluated a marketing application's proposed manufacturing, drug substance, and drug product specifications by relying on the developmental work and the clinical batch history. The challenge is that often there are only a few clinical lots, especially if the marketing application was submitted under an accelerated developmental program. Limiting the evaluation criteria to the clinical batches does not take into consideration the process understanding or prior knowledge from similar products, animal

ISPE's Regulatory Affairs function

ISPE's Regulatory Affairs function plays a vital role in the Society, which is to build effective relationships with regulators and agencies globally and ensure all members have access to the latest regulatory developments and expectations. These activities are driven by the collective efforts of ISPE member volunteers, advisors, and staff who monitor current trends and facilitate the translation of regulatory expectations into practical solutions delivered through ISPE products and services.

ISPE's volunteer committees are comprised of the following groups.

Regulatory Steering Council (RSC)

The RSC establishes ISPE's global regulatory priorities in support of ISPE's Strategic Plan. The RSC provides a forum for facilitating discussion and alignment on regulatory topics and acts as an advisory council to ISPE leadership on responding to emerging regulatory opportunities. In recent months, the RSC has contributed to ISPE's input on the European Medicines Agencies' Network Strategy to 2021 [1], an ISPE report on Increasing Domestic Resiliency in Supply of Essential Active Pharmaceutical Ingredients [2], and feedback to the Pharmaceutical Inspection Co-operation Scheme (PIC/S) on their 2022–2026 Strategic Plan.

Regulatory Quality Harmonization Committee (RQHC)

The RQHC supports ISPE in sustaining its understanding of the global regulatory environments. The committee is structured in four regional focus groups and a global management team. The regional focus groups—Asia-Pacific, Europe-Middle East-Africa (EMEA), Latin America, and North America—provide ISPE with intelligence on regulatory topics and issues of concern in their respective regions and recommend approaches for ISPE's involvement or response (for example, establishing a working group to develop a paper, conference session, etc.). Current areas of focus for the regional groups include:

- European Commission EudraLex GMP Guide: Annex 11 and Chapter 4 [3]
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q9 revision
- PIC/S Annex 2: GMP for ATMP (presentation to be delivered at the ISPE Biotechnology Conference on 22 September)
- Regulatory Challenges of Cell & Gene Therapy (presentation to be delivered at the ISPE Annual Meeting & Expo on 1 November)
- Remote/Distant Assessments
- Risk-based Quality Overall Summary (presentation to be delivered at the ISPE Annual Meeting on 2 November)
- Regulatory updates published on the ISPE website [4]

The RQHC's management team, which is referred to as RQHC Global, acts a forum where the Regional Focus Group leaders discuss emerging regulatory topics and coordinate any resulting activity. RQHC Global also is tasked with overseeing ISPE's comments to health authorities on documents released for public consultation, ensuring the feedback is representative of ISPE membership. Commenting opportunities for members are announced on the Regulatory/Quality Networking Community [5].

In addition to the standing committees described above, ISPE initiative teams address high-profile, cross-industry topics. Current initiative teams include the following.

Advancing Pharmaceutical Quality (APQ)

The APQ initiative team is developing a program by the same name that provides a practical framework for companies to use to assess the maturity and advance the state of quality within their organizations. It is an industry-for-industry program aligned with ICH Q10 principles that aims to identify the practices and behaviors which support the continual improvement of quality within an organization. The APQ Program is being delivered through a series of guides [6].

- *Corrective Actions and Preventive Actions* (CAPA) (published 2020)
- *Management Responsibilities and Management Review* (published 2021)
- *Process Performance and Product Quality Monitoring System* (expected to publish in 2021)
- *Change Management System* (expected to publish in 2022)

Each guide includes detailed diagnostic tools for assessing and potentially improving a company's maturity in the specific element, and also includes a pre- and post-assessment benchmarking exercise developed by the University of St.Gallen which can be used to measure progress. The APQ team has had several communication exchanges with global regulators during the program's development. A session focused on the APQ program will be held at the ISPE Annual Meeting on 1 November.

Drug Shortages

Any effort to effectively address the complex and multifaceted issues contributing to drug shortages (DS) requires close technical collaboration and clear communication between the pharmaceutical industry and global health authorities. ISPE's Drug Shortages initiative began nearly 10 years ago with comprehensive research into the manufacturing and quality related causes of DS, and the subsequent publication of guides and tools to help industry build capability in the areas found critical to creating resilient supply chains.

The ISPE Drug Shortages Initiative Team is now entering a new phase of work focused on business continuity planning for the prevention of DS. The COVID-19 pandemic amplified the need for robust and resilient supply chains, which in turn is prompting the introduction of new and evolving regulations related to DS prevention planning. The team recently conducted a survey to obtain an understanding of the state of business continuity plan for drug shortage prevention. They are analyzing the findings and will use them to prioritize and develop activities to further support the industry with business continuity planning and comply with the new and evolving health authority expectations. The team is hosting a regulator discussion panel webinar on 28 September, which will lead into a discussion of preparing proactively for potential drug shortages at a session at the ISPE Annual Meeting on 1 November.

Product Quality Lifecycle Implementation (PQLI®)

The Product Quality Lifecycle Implementation (PQLI) initiative was created to provide guidance on practical implementation of the concepts described in ICH guidelines, focusing on Q8, Q9, Q10, Q11, and Q12 to help ensure product quality throughout a product life cycle, leading to continuous product improvement. PQLI concepts have been foundational to advancing science- and risk-based approaches across the product life cycle to achieve excellence in drug development and pharmaceutical production.

For more information

News of ISPE's regulatory and quality activities is reported in the *Regulatory Digest* quarterly e-newsletter, and on the ISPE website. For more information or for inquiries on joining any of the groups, contact Carol Winfield, ISPE Senior Director of Regulatory Operations, at cwinfield@ispe.org

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— Carol Winfield, ISPE Senior Director, Regulatory Operations

studies, publications, and process controls/attributes risk that are also relevant to the product quality.

In the past three years, this PQLI team has been involved with sharing the patient-centric specifications topic in different conferences and forums [19]. The feedback from the presentations has been very positive from the pharmaceutical community and the regulatory attendees. Pharmaceutical company representatives acknowledge that they have all faced the same challenges to obtain a globally accepted specification approach, which has resulted in complexity within the pharmaceutical companies' regulatory and operations groups to support the divergent marketing application details. The FDA has also acknowledged that a patient-centric specification approach is acceptable. In fact, the FDA has created an internal procedure document for their assessors to drive a more consistent approach in determining approvability of specifications and controls based on all of the relevant data and not just on the manufacturing history [20]. However, the team fully recognizes that to be successful, patient-centric approaches need to be adopted worldwide.

As the team looks to continue the conversations about this topic, they are focused on three goals. The first goal is to host an ISPE webinar to broaden exposure to the topic to ex-US regulatory agencies. An FDA representative will also be among the speakers to provide the regulators' perspective. Second, the team plans to publish a discussion paper in support of changing the ICH Q6A/B documents' language to be consistent with the patient-centric specification approach. Part of the confusion about appropriate specifications can be attributed to the current language in both ICH Q6A and 6B [21, 22], which are now over 20 years old. Some of the text is conflicting even within the guidance documents when viewed from a patient-centric perspective. In contrast, more recent ICH guidelines, such as ICH M7 on mutagenic impurities and ICH M9 on biowaivers, have elements that are consistent with patient-centric specification setting. Finally, the team is looking to continue to advance the topic through publications. The PQLI Working Group published a paper for small molecule considerations of patient-centric quality standards [23] and is working on a paper specific to biologic specification setting. Even though new biological entities are more complex than their small molecule new chemical entities, there are still opportunities to support a patient-centric approach in the biologics marketing applications.

PQLI Process Validation Working Group

The Process Validation (PV) Working Group is the most mature of the PQLI teams; it was founded about 10 years ago and remains very active. The PV team is focused on the practical implementation of life cycle approaches to PV. Because of its broad nature, PV has natural linkages to many other PQLI and ISPE topics under development.

Initially, the team was focused on understanding challenges in practical implementation of PV to the product life cycle arising out of the regulatory guidance such as the FDA's 2011 Process Validation guide [24]. Questions addressed included use of statistics, implementation of control strategy, planning and management of continued/ongoing process verification, application of PV to legacy products, and techniques to determine the number of batched required for process performance qualification (PPQ).

The PV team has been active in presenting best practices from ISPE member organizations, hosting work groups and discussions on challenging topics, and disseminating information through published articles and presentations. The team has published nine discussion papers over the past decade covering a wide range of PV-related topics, including "Stage 3 Process Validation: Applying Continued Process Verification Expectations"; "Lifecycle Approach to Biotech Process Validation"; "Implementing Lifecycle Validation Practices at Contract Manufacturing Organizations"; "Determining Number of Process Performance Qualification Batches Using Statistical Tools"; and "Process Validation in Context of Small Molecule DS and DP Continuous Manufacturing Processes" [25]. These discussion papers are provided free to ISPE members.

The PV team regularly holds sessions at the ISPE Annual Meeting on PV-related topics. Additionally, the team has conducted five well-attended stand-alone PV workshops between 2012 and 2019, where both industry SMEs and regulators shared their experience on this subject. Despite PV being a more mature topic, there is still enormous demand for some of the original concepts developed by the team, especially in a webinar format. Members of the PV team developed ISPE's Process Validation Training course and have contributed to many regulatory and affiliate conferences around the world. ISPE instructors have also provided multiple trainings to regulators worldwide on PV topics.

In 2019, a subgroup of the PV team authored ISPE's *Process Validation Good Practice Guide* [26]. This guide built on the work of the team and contains practical guidance covering all three stages of the PV life cycle as it is interpreted worldwide. It discusses PV in the US and EU and in emerging markets such as Asia Pacific and other parts of the world. The guide contains six detailed appendices covering case studies and application of statistical techniques to PV.

The PV team is still very active, with 50 members that meet monthly. The team continues to work on evolving new PV content and delivering knowledge. Topics of current interest include applying science- and risk-based thinking to emerging PV challenges for new modalities such as cell and gene therapy, products under accelerated development, and continuous verification.

CONCLUSION

Although much has changed since PQLI was initiated, one constant is the ability of PQLI technical teams to advance new regulatory approaches based on current science and technology. The life cycle aspect of PQLI covers not only pharmaceutical product life cycle, but also the life cycle for the technical teams themselves. New topics are added to PQLI as they emerge and sunsetted as they mature into standard practice. The chairs of PQLI and the team leads welcome ideas for new topics and nominations of experts

who are ISPE members and willing to contribute to technical teams. ISPE members with deep subject matter expertise should contact Regulatory@ISPE.org if interested in participating in PQLI teams as contributors.

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Wyatt J. Roth, PhD, is a Director within the small molecule design and development organization at Eli Lilly and Company, Indianapolis. He received BS degrees in pharmaceutical sciences and agricultural and biological engineering and his PhD in industrial and physical pharmacy from Purdue University. After joining Lilly, Wyatt led continuous manufacturing feasibility and process optimization studies, which influenced the decision to build Lilly's first GMP drug product CM facility. Since that time, he has served as the lead development scientist for Lilly's first two assets that used a CM. Wyatt has expertise in control strategy development and technical transfer from development to commercial manufacturing sites for continuous direct compression manufacturing processes culminating in the approval of Lilly's first drug product using a CM platform. Wyatt has been an ISPE member since 2020.

Eli Zavialov, PhD, is Scientific Director, Regulatory CMC Dossier Development and Operations at J&J. Eli joined Johnson & Johnson in 2011, where he made significant contributions to the preparation and delivery of technical CMC sections to support global clinical trial and marketing applications across a diverse portfolio of biologics and small molecules. Eli serves as a single point of contact for GRA CMC senior leadership on strategic dossier needs and requirements. Eli works in close partnership with GRA CMC and matrix functions to ensure that dossier submission projects are aligned with key stakeholder requirements. Eli previously worked in chemical development and technical operations at Merck and Schering-Plough. Eli holds a BSc in chemistry from Moscow State University, Moscow, and PhD in organic and bioorganic chemistry from the University of Southern California. He joined ISPE in 2019.

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ISPE Japan Affiliate: Growing to Meet Market Needs

By Marcy Sanford

Japan's pharmaceutical market is one of the world's largest and the ISPE Japan Affiliate is helping its members stay connected and current in the ever-changing pharmaceutical industry.

With a population of more than 126 million, Japan is the third largest pharmaceutical market in the world [1]. According to figures from the Ministry of Health, Labour, and Welfare's Annual Pharmaceutical Production Statistics, the Japanese market for prescription and nonprescription pharmaceutical products in 2019 totaled $105 billion, up 18 percent from 2018. Imports of foreign pharmaceuticals accounted for approximately 30 percent of the total Japanese market [2].

Although Japan's population has started decreasing over the past 10 years, it continues to have one of the world's highest life expectancy rates and its pharmaceutical market is expected to remain one of the strongest worldwide due to continued demands for innovative therapies. Antitumor agents are among the top selling pharmaceuticals in the country [2]. Other top sellers include diabetes agents, antithrombotic agents, immunosuppressants, and ophthalmic agents [2]. Pharmaceutical companies continue to enter the Japan market including Takeda, Daiichi Sankyo, Pfizer, Chugai, Astellas, Otsuka, MSD, Mitsubishi Tanabe, GSK, and Novartis. [3]

A GROWING MARKET

"Japan occupies one of the few global drug development bases and the stable supply of medicines for our citizens is the responsibility of the pharmaceutical industry," said Ayako Nakajima, ISPE Japan Affiliate Past Chair. "The promotion of innovation in the industry in Japan will continue. However, in order for the pharmaceutical industry to drive the Japanese economy as one of the growth industries, the new drug market here must be as attractive as the ones overseas." Nakajima said strategies in place to strengthen the pharmaceutical industry in Japan include efforts to:

- Improve the research and development environment
- Reduce cost and improve efficiency through regulatory reforms
- Improve pharmaceutical productivity and manufacturing infrastructure
- Develop an environment and infrastructure for proper evaluation
- Promote international expansion of Japanese drugs
- Create global ventures that promote the growth of the drug discovery industry
- Improve distribution of medical drugs

AFFILIATE INITIATIVES

Formed in 2002, the ISPE Japan Affiliate strives to meet the educational and networking needs of its members by offering a comprehensive program of continuing education seminars and conferences for pharmaceutical professionals. The Affiliate has translated 41 ISPE Guidance Documents into Japanese, and written a *Pest Control Manual*.

"ISPE's Guidance Documents provide a huge value to our members and lead them in the right direction when they have questions," said Nakajima. "You also learn a lot when you work on the translation of one of the ISPE Guides."

During the COVID-19 pandemic, the Japan Affiliate like many others had to change from in-person to online activities. But they were able to continue to provide robust programming for their

members, which helped them have an almost 75 percent renewal rate among members. Because of this renewal rate, the Affiliate won third prize in the ISPE October 2020 Member Renewal Contest. "We began contacting our members three months before it was time for them to renew and our board is continually considering new ideas to encourage membership renewal as well as ways to entice new members to join," said Nakajima.

Offerings the Japan Affiliate provides to its members include:

- 12 conferences, technical webinars, plant tours, or networking events each year
- 15 Communities of Practice (CoPs) that meet monthly to work on projects
- Ongoing opportunities to connect with regulators, academia, and industry members.

Japan Affiliate members were able to hear a presentation from Lawrence Yu, Deputy Director, Center for Drug Evaluation and Research's Office of Pharmaceutical Quality, US FDA, at the Affiliate's Annual Meeting in May. Typically held in person, this year's annual meeting was held virtually with more than 300 attendees. The theme was "Pharma Society 5.0 'Moonshot'–Our Strategic Path Forward." In addition to guest speakers from regulatory agencies, academia, and industry, workshops were provided by the Affiliate's CoPs.

FUTURE PLANS

The Affiliate is planning a Winter Meeting in December in Osaka to focus on cutting-edge technologies, and is hoping to bring back their popular US Pharmaceutical Plant Tour in 2022.

Nakajima said that the board encourages Affiliate members to give feedback about the topics they are interested in learning more about so that the board can best determine which educational opportunities to provide. One of the most popular recent webinars covered the topic of remote inspections.

"Next, we are planning to publish a newsletter via email in order to keep our relationships strong, share valuable information on time, and to compensate for the lack of communication under COVID-19. Webinars, electronic information sharing, and web networking have worked very well to keep and increase our membership."

In addition to providing members with educational opportunities, the Japan Affiliate has an Emerging Leaders group, a Women in Pharma® Mentor Circle, and hosts plant tours for students to interest them in the pharmaceutical industry. Nakajima said these groups serve not just to educate but to encourage and inspire.

"Our goals with ISPE are to share international knowledge, to develop young talent, to improve our own expertise and share information with others around the world, and to contribute globally to the development of the pharmaceutical industry."

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About the author

Marcy Sanford is the Editorial Assistant for ISPE's Publications Group.

Quick Facts about the ISPE Japan Affiliate

- **Founded:** 2002
- **Region:** Asia Pacific
- **Membership:** 727

Officers

- **Chair:** Hiroshi Yamaguchi, Fresenius Medical Care
- **Vice Chair:** Hiroshi Sakai, Kokando Co., Ltd.
- **Treasurer:** Tetsuro Noguchi, Nobelpharma Co., Ltd.
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ISPE BRIEFS

New APQ Guide on Management Responsibilities and Review

By Marcy Sanford

The second guide in ISPE's Advancing Pharmaceutical Quality (APQ) series provides a systematic and proactive approach to quantitatively assessing and advancing leadership systems by evaluating the management responsibilities highlighted in ICH Q10 as well as other key leadership components.

The *ISPE Advancing Pharmaceutical Quality: Management Responsibilities and Management Review* Guide "builds upon the foundation of ICH Q10 and adds other key leadership components such as creating a strong patient/consumer focus and establishing systems and staff for external surveillance, engagement, and benchmarking," said guide Co-Lead Steven A. Greer, Executive Coach, Speaker and Consultant, Genesis Assist, LLC and ESi, Inc. "This guide provides a practical tool for organizations that want to assess and strengthen their leadership systems to support their pursuit of cultural excellence and ultimately create more value for their patients, shareholders, and employees."

"Most leaders of pharmaceutical organizations are committed to quality but determining how that commitment positions the organization for success in achieving and sustaining cultural excellence can be difficult," said guide Co-Lead Michael Grischeau, Director of Data Analytics and Management Review, AbbVie, Inc. "Most scorecards do not include metrics focused on leadership effectiveness so drift can occur without warning signs and the results can be significant: drug shortages, enforcement actions, recalls, dissatisfied patients/consumers, and disengaged organizations. The APQ Guide builds on the framework of ICH Q10 with insights from industry leaders on what strong and effective leadership looks like."

Part of ISPE's Advancing Pharmaceutical Quality initiative, (https://ispe.org/initiatives/quality-metrics), the APQ Guide Series is aligned with international programs that promote quality excellence, as well as the FDA's interest in quality management maturity. The ISPE *APQ Guide: Corrective Action and Preventive Action* was the first in the series and published in 2020. Two future guides in the series will explore (a) change management and (b) process performance and product quality monitoring systems.

For more information about the guide, visit ispe.org/publications/guidance-documents

About the author

Marcy Sanford is the Editorial Assistant for ISPE's Publications Group.

MEET THE ISPE STAFF

SINDY GIRON

In each issue of *Pharmaceutical Engineering*®, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Sindy Giron, Administrative Assistant to Thomas Hartman, President and CEO of ISPE. She is in the Administration Group.

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

As an Administrative Assistant to Thomas Hartman, my role is to provide administrative support on a daily basis. Some of my responsibilities include assisting with planning and scheduling meetings and coordinating the CEO's calendar and other activities necessary to ensure success. I provide general support to the ISPE North Bethesda, Maryland, office staff. Additionally, I maintain a consolidated Master Activity Sheet including member engagement plans such as conferences, training, webinars, and related digital experiences. I am responsible for the development of ISPE Leadership Team meeting agendas and support the development of the Staff Engagement Agendas for all staff meetings. I also provide periodic and focused support to the Regulatory and Training Departments.

What do you love about your job?

I love the work environment and how ISPE employees are always willing to help others to ensure ISPE's success.

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

I love to spend time with my family and travel.

PHARMACEUTICAL CLEANROOM DESIGN and ISO 14644-16

By Emilio Moia

Cleanrooms and controlled contamination environments are increasingly being used across many industrial sectors, including the pharmaceutical industry. An important issue is the operating cost associated with cleanroom energy consumption and, consequently, the identification of applicable energy containment measures. This article reviews pharmaceutical cleanroom calculations for non-unidirectional airflow against energy consumption with known sources of contamination and type of air diffusion used. It proposes alternative cases to compare potential economic savings from applying energy-saving measures proposed by ISO 14644-16 [1].

Pharmaceutical cleanrooms can consume up to 15 times more energy than commercial building systems, with more than 50% of electricity being consumed by plant HVAC cleanroom systems [2]. This level of energy consumption is driven by the high air change rates required to ensure the air quality of pharmaceutical production.

Typically, there are two ways to control airborne contamination: a displacement system with unidirectional airflow (UDAF) or a system providing dilution, non-UDAF. Because systems that use UDAF systems have very high airflows, they are not considered here.

When designing a cleanroom with non-UDAF flow, it is important to ensure:

- Environmental contamination is below the limits defined in the user requirement specification (URS).
- The HVAC system is able to control thermal loads to meet temperature and relative humidity environmental requirements.
- The external airflow rate is adequate to maintain space pressurization to compensate for leakage from/to the cleanroom and to account for process air discharge/consumption.
- The airflow rate is sufficient to ensure that the time of cleanroom cleanup is below defined limits. (This requirement is applied to the pharmaceutical cleanroom to ensure compliance with European GMP [3].)

The energy efficiency of the cleanroom, including the HVAC system, is subordinate to the reliability and performance of the pharmaceutical process. During the design phase of the cleanroom, the extent of the contaminant source is unknown. To define the airflow rate, designers often rely on industry guidelines. This choice can lead to oversizing the HVAC system, which results in high capital and operating costs.

ISO 14644-16, Part 16, "Energy Efficiency in Cleanrooms and Separative Devices" [1], prescribes a set of recommendations for energy efficiency in cleanrooms and the optimization techniques applicable in every stage of cleanroom life, including airflow rate design.

ENERGY-SAVING METHODS

The following methods can be applied to reduce energy consumption in cleanrooms:

- Minimizing cleanroom size.
- Avoiding overspecification of the contamination class.
- Installing low-pressure drop HEPA filters.
- Reducing make-up air due to air leakage between two rooms at different pressures, sealing the cleanroom structure (walls, terminal HEPA filters, lamps), and sealing and testing air ducts.
- Minimizing the number of people in the cleanroom. This can be accomplished with technologies that require the presence of a reduced number of operating personnel, such as processes with closed systems, restricted access barrier systems (RABS), and isolators. (A comparison between RABS and isolator technology and relevant operating cost was presented during an Associazione per lo Studio e il Controllo della Contaminazione Ambientale [Italian Association of Contamination Control] conference [4].)
- Properly selecting consumables used in cleanrooms and operator clothing.

- Reducing the airflow during the at-rest condition of the cleanroom.
- Avoiding overdesign of airflow rates.

REFERENCE STANDARDS FOR AIR CHANGES

Many cleanroom regulations and standards do not specify air changes and leave it to the project designer to analyze and define these values, which are important cleanroom design parameters. However, research of regulations and standards documents found a guidance value of 20 air changes per hour (ACH) and a guidance time of 15–20 minutes for cleanup (also called recovery) time. (Table 1 shows the recommended values of air changes across various standards [3, 5-7].)

For Class 100,000/ISO 8 supporting rooms, airflow that is sufficient to achieve at least 20 ACH is typically acceptable. Significantly higher ACH rates are normally needed for Class 10,000/ISO 7, Class 1,000/ISO 6, and Class 100/ISO 5 areas [5].

The World Health Organization (WHO) 2019 technical report for nonsterile drugs states, "The number of air changes or air-exchange rates should be sufficient. A guidance value is between 6 and 20 air changes per hour." It further outlines that manufacturers should establish "how much time it takes for a room that is out of its classification to return within the specified class," which is often referred to as cleanup or recovery time, and offers a guidance period of 15–20 minutes [7].

In the latest revision of the EU GMP [4], the indication on minimum air changes was removed, but the guide retained the requirement of a "cleanup period" of 15–20 minutes.

The ISPE *Baseline Guide*, Vol. 3, *Sterile Product Manufacturing Facilities* [7] makes explicit reference to the *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning* [6]. The latter publication defines the air changes to be applied during the conceptual design phase with the intention to revise and reduce them in the next phase—detail design—when more detailed information about process operation and personnel (number of operators, type of garments worn) will be available.

AIRFLOW IN CLASSIFIED ROOMS

ISO 14644-16 [1] dedicates chapter 6 to the calculation of the airflow rate, highlighting that the airflow contributes significantly to the cleanroom's energy consumption. Therefore, a reduction of airflow rate leads to significant energy savings. In fact, the ventilation power by fans depends on the cube of the airflow rate:

$$\frac{P_1}{P_2} = \left(\frac{Q_1}{Q_2}\right)^3$$

Where P is power in watts and Q is flow rate in m^3/s.

The standard introduces the types of air diffusion, the UDAF that removes the airborne contamination by displacement, and the non-unidirectional flow (air mixing, non-UDF) that reduces airborne contamination by dilution. It also describes the method to calculate the airflow for non-UDAF to dilute the airborne contaminants. The equation adopted for the calculation is reported in Annex A [1]:

Table 1: Recommendations for air changes in various guidelines.

Source	Sterile Production	Nonsterile Production
• USA FDA aseptic guidance [5]	• 20 ACH	
• EU GMP [3]	• Cleanup period 15–20 min	
• ISPE *Good Practice Guide: Heating, Ventilation, and Air Conditioning* [6]	• 6–20 ACH for CNC (EU Grade D) spaces • 20–40 ACH for Grade 8 (EU Grade C) spaces • 40–60 ACH for Grade 7 (EU Grade B) spaces	
• WHO [7]		• 6–20 ACH

$$Qs = \frac{D}{\varepsilon * C} \qquad \text{Equation 1}$$

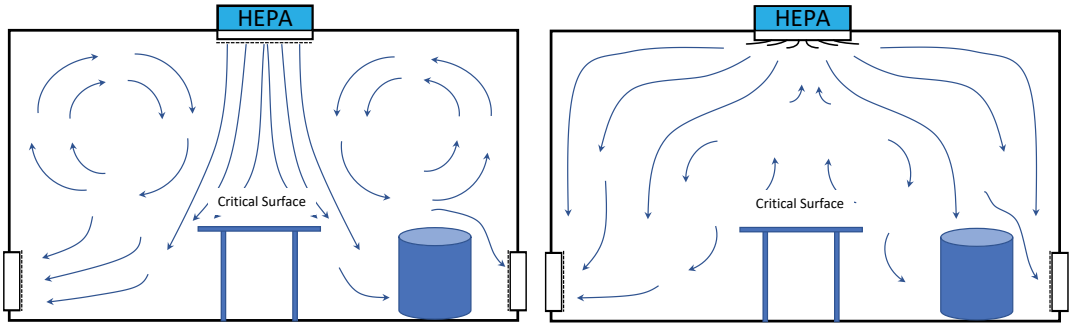
Where Qs is flow rate (m^3/s); D is the rate of emission of particles or microbe-carrying particles (MCPs) from sources of contamination (counts/s); C is the limit of particles/m^3 or MCPs/m^3 in the environment; and ε is ventilation efficiency.

Due to the uncertainty of the data at the design stage, the standard suggests adopting a compensation factor, expressed in paragraph 6.3.3 as follows [1]:

> *a) as a margin for particle concentration limit alert levels, for example, ISO 7 class limit, C_{class}, is 352,000 particles/m^3 for particles ≥ 0.5 µm, but, for process reasons, its alert level, C_{lim}, can be chosen as 100,000 particles/m^3, or even 50,000 particles/m^3; and b) as a margin for particle removal effectiveness by lowering the predicted CRE [contamination removal efficiency] or ACE [air change effectiveness] to values less than 1.0 if air distribution is deemed to be not good enough.*

Several studies regarding the sources of contaminant emissions were carried out by Ljungqvist and Reinmuller. In an interesting article, Romano and colleagues [9] evaluate emissions from personnel, determine the main source of contamination, test different types of clothing worn by operators, and simulate different movements of the operator in a cleanroom. Chapter 5.2 of ISO 14644-16 establishes that "the required cleanroom garment levels should also be specified in the URS since they play a vital role in controlling particulate contamination" [1].

Figure 1: A HEPA filter without a diffuser (left) and a HEPA filter with a diffuser (swirl diffuser; right).



The emission of MCPs from process equipment is usually considered negligible. However, the process equipment supplier should provide data for the emission of nonviable contaminants. If this information is not available, ISO 14644-16 mentions that ISO 14644-14 [10] describes a method to determine the emission of particles from equipment. (The literature provides measured values of particle emissions from some process equipment [11].)

In relation to ventilation efficiency, ISO 14644-16 specifies two types of ventilation efficiency: CRE and ACE. ACE is determined according to ANSI/ASHRAE 129-1997 [12], which relates the nominal time constant to the age of the air at a point:

$$\text{ACE} = \frac{\tau_n}{A_i} \qquad \text{Equation 2}$$

Where τ_n is the nominal time constant, equal to 1/N (room air changes), and A_i is the air age at measuring point, equal to $1/n_i$ (local time changes).

Whyte [13] demonstrated that the ACE value can also be calculated as the ratio between the air changes at the measuring point and the nominal air changes in the room. The air changes can be calculated from the particle decay as follows:

$$n = -\frac{1}{t} * l_n \frac{C}{C_0} \qquad \text{Equation 3}$$

Where t is the time to switch from initial concentration, C_o, to final concentration, C.

Then the value of ACE is calculated as:

$$\text{ACE} = \frac{\text{Recovery time measured at 1 point}}{\text{Room air changes}}$$

The CRE ventilation efficiency is calculated as follows:

$$\text{CRE} = \frac{\text{Airborne particle concentration at exhaust}}{\text{Average airborne pacrticle concentation in the room}}$$

Though the ASHRAE standard defines how to measure and calculate the ACE value, there is no standard for the CRE value.

The CRE coefficient is used when the contamination comes from a precise, fixed source. The CRE index gives information about the ability of the ventilation system to control the contaminants emitted from a specific source but does not provide any information about the efficiency of the cleanroom's ventilation system, and it cannot be used to predict the level of airborne contamination that could be reached in the cleanroom.

Considering that the source of contamination in a cleanroom is not always located at a fixed point (for example, the operators in cleanroom), the suggestion is to use the ACE index to calculate the airflow rate.

ISO 14644-16 Appendix A.2.2 states that, "in the majority of cleanrooms, the main contamination problem is caused by personnel who move freely about the room. In that situation, the aim should be to ensure that sufficient contamination-free air reaches the critical location(s) to ensure the required concentration of contamination" [1].

The air diffusion system should be designed to reach an ACE index as close as possible to 1, the perfect mixing. If the value is less than 1, it means that less "clean" air reaches the point of measurement, whereas if the value is greater than 1, it means that more "clean" air reaches that point.

The ACE index depends on the type of air diffuser. Figure 1 shows a HEPA filter with and without a diffuser. (ISO 14644-16 defines a diffuser as a "device placed on inlet air supply terminal to improve distribution of incoming air with room air. A mesh grille or a perforated screen is not considered to be a diffuser" [1].)

In a diffusion air system with a HEPA filter without a diffuser, most of the air is supplied directly under the HEPA filter, where the cleanliness level is greater than in the rest of the room. Accordingly, the ACE index under the filter shall be greater than 1, whereas in the rest of the room it will be less than 1. In this situation, the air diffusion shall not be homogenous with consequent nonhomogeneous particle concentration in the cleanroom, and nonhomogeneous room volume temperature. The nonhomogeneous room temperatures may cause discomfort for operators and, more importantly, may lead to uncontrolled air currents in the cleanroom, increasing the risk of product contamination.

If the same degree of cleanliness is required throughout the room—a necessary condition when the emission sources of contaminants are not fixed in space and time—air diffusion with a HEPA filter without a diffuser would not be the most suitable option. Air diffusion with a HEPA filter without a diffuser creates a sort of unidirectional flow, which is required when a higher cleanliness class is necessary to protect a zone locally—for example, the point of the vessel loading in a preparation room.

In summary, in a cleanroom with non-UDAF, the supply airflow is calculated with equation 1, where the ACE index is determined with consideration given to:

- Type of diffuser
- Performance of diffusers that normally create good air mixing in the room but operate at higher or lower speeds than the design
- Generation of uncontrolled air currents due to the supply air being warmer or colder than the cleanroom, and consequent uncontrolled air currents in the cleanroom volume [14, 15]
- Presence of fixed emission sources (process equipment that emits particles, workplaces where heavy activity by the personnel is required)
- Possible obstructions due to the presence of process machines or various equipment, such as vessels, which limit the air penetration in some areas of the cleanroom with phenomena of short circulations of the air between the supply and the air return

It is also worth considering Eaton's analysis of cleanroom contamination measurements [16], where, after verifying the contamination class of the room according to ISO 14644-1 (2015 version) [17], it was found that the contamination value was above the limit at a point. Following this, the ACE index was verified at each point of the cleanroom, and at the point where the contamination was very high, the ACE index was much lower than 1, meaning there was bad air distribution in proximity of a source of particle emission [16]. In conclusion, it is reasonable for the calculation of the airflow to consider an ACE value of 0.7 when the air is supplied in the cleanroom with high-induction diffusers and is extracted through floor-level return.

Thus far, the airflow rate has been calculated using equation 1, which considers cleanroom contamination sources. But pharmaceutical cleanrooms must also satisfy the "cleanup" period requirement, as indicated in the EU GMP Guide, Annex 1 [3]. The cleanup period can be calculated using equation 3, integrated with the ACE index, as follows:

$$n = -\frac{1}{t} * (l_n \frac{C}{C_0}) * \frac{1}{\text{ACE}} \qquad \text{Equation 4}$$

Having defined the cleanup period, this equation can also be used to calculate the airflow for an air lock, material, or personnel.

Table 2 presents the results of the airflow calculated with equation 1 (dependent on the source of contamination) and equation 4 (dependent on cleanup period). The airflow due to cleanup period is greater than the airflow due to contamination sources (airflow is expressed as air changes).

Table 2: Calculation of the supply airflow for a Grade C cleanroom.

Cleanroom surface (m^2)	100		
Cleanroom volume (m^3)	300		
	Nonviable 0.5 µm	**Viable MPCs**	**Cleanup Time**
EU GMP Grade C limit (operational): Airborne contamination, cleanup time	3,520,000 part/m^3	100 MCP/m^3	15–20 min
Alert limit/m^3 (considering a compensation factor of 30% of the limit)	1,000,000	35	
Cleanup period limit			15 min C = 352,000 C_0 = 3,520,000
Total particle and MPS dispersion rate per second, due to 10 people (emission rate per person: 15,000 part/s of 0.5 µm, and 2 MCP/s)	150,000	20	
ACE	0.7	0.7	0.7
Calculated air change, ACH	2.6	9.8	13.2

Note: The higher air change shown in the table (13.2 ACH) is lower than the minimum US FDA–required ACH (20 ACH) [5].

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Figure 2: HVAC system diagram.

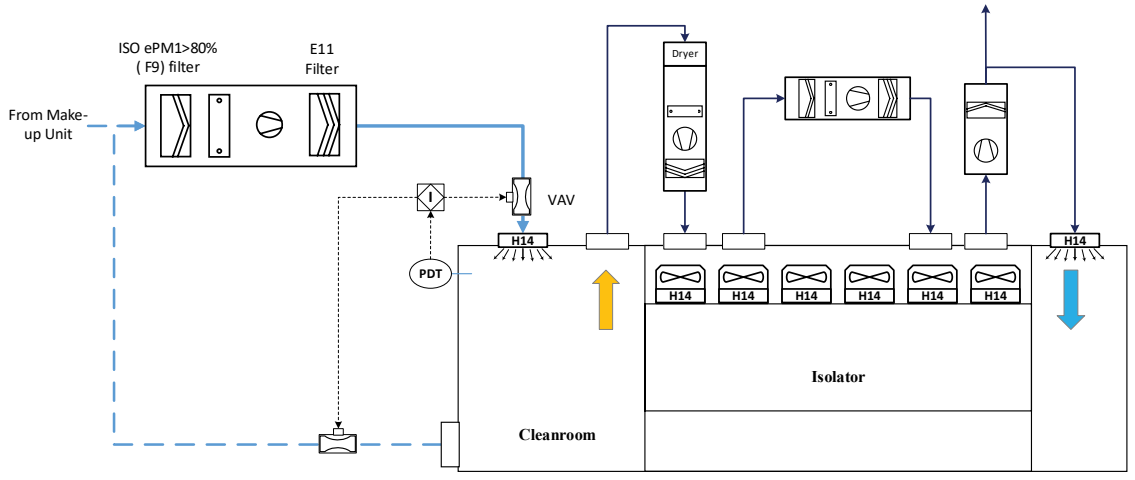

Table 3: Cleanroom energy-saving strategy with variable airflow.

	HVAC System in Operational Mode	HVAC System in Attenuation Mode (At Rest)
Airflow reduced percentage	100%	50%
Supply airflow rate (m^3/h)	10,000	5,000
Total HVAC system pressure drop (Pa)	1,150	670
Fan efficiency	75%	70%
Fan power (kW)	4.3	1.3
At-rest condition total hours/year	3,900	3,900
Total blowing energy (kWh/year)	16,601	5,181
Blowing energy saving (kWh/y)	11,420	
Electric energy cost (Euro/kWh)	0.12	
Operating expense saving (Euro/year)	1,370.4	

CLEANROOM ENERGY COSTS

It is common for cleanrooms' HVAC systems to be in continuous, 24/7 operation, even during nonoperational (at-rest condition) hours when a reduction in airflow rates would allow energy savings (unless, of course, the room cleanliness is compromised).

Table 3 shows the estimated annual energy and cost savings of a cleanroom designed to reduce the airflow rate during the at-rest period.

In Chapter 7 of ISO 14644-16, there is a focus on the cleanroom parameter, in particular on the room pressure that "should be maintained to prevent ingress of contamination from the surrounding area into the cleanroom or clean zone" [1]. This requirement is consistent with the Chapter 53 of the EU GMP Annex 1 [3], which states, "A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively." Therefore, the HVAC system and relevant pressure control loop should be designed to avoid any peaks of room pressure out of the limit, positive or negative, even when the cleanroom is transitioning from operating mode to reducing mode, or vice versa.

One strategy to reduce the airflow rate could be to smoothly adjust the set-point values of the HVAC system's variable air volume (VAV) air valves and combine the airflow tracking with the room pressure sensor that, if necessary, adjusts the offset of the airflow track to keep the room pressure differential at the desired level. The supply and return VAV air valves must be selected considering the accuracy of the flow measurement and relative errors [18].

Figure 2 presents an example of a cleanroom pressure control for a filling room with isolator; the VAV system has been carefully selected to control the room pressure in all phases of the isolator operation.

ENERGY-SAVING OPPORTUNITIES

Annex B of ISO 14644-16 [1] lists the energy-saving opportunities, with the different opportunities organized by stage of implementation:

- Source strength evaluation
- URS
- Design, redesign, and construction
- Testing
- Operation and maintenance
- Cleanroom disposal (decommissioning)

Annex C of ISO 14644-16 [1] states that "a careful assessment of the impact and consequences of any proposed energy optimization change should be carefully addressed in the context of the fundamental principles of establish control and then demonstrate control." It further outlines that assessment factors should include contaminants; people variability and uncertainty (people are a highly variable source strength of contamination; and people density, gowning, and cleaning are significant factors to consider); and process variability. Also reviewed and considered were Annex D, "Benchmarking: Energy Performance Indicators for Cleanrooms," and Annex E, "Useful Measures to Minimize Excess Heating and Cooling Losses or Gains."

The following examples and Table 4 illustrate energy savings associated with the saving of make-up air (the annual cost of make-up air of a pharma cleanroom ranges between 1.5–2.0 Euro/[m^3/h]) and the saving of energy for cooling and heating of air supply.

- Example 1, saving make-up air, improving the duct air tightness: Designing the ductwork with a good air tightness (class ATC 3 according to EN 16798-3 [6]), compared to normal air tightness duct (class ATC 4 according to EN 16798-3) may save 2% of make-up air (that is, 1,500 Euro/year operating cost saving for a supply air of 50.000 m^3/h).
- Example 2, saving make-up air, shaping the opening of conveyor belt: By reducing the dimension of the opening from original size of 0.2 × 0.2 m to 0.1 × 0.1 m, shaping the opening around the vials, with a differential pressure of 15 Pa, it is possible to reduce four times the airflow through the opening. The airflow across the opening is calculated with the equation:

$$Q\left(\frac{l}{s}\right) = 840 * A(\mathrm{m}^2) * \sqrt{Pa}$$

- Example 3, avoiding the overlap of cooling and heating of supply air: An excess of air cooling of 1°C given by the cooling coil of the recirculating unit means an additional heating of 1°C of the duct reheating coil. For a supply air of 10,000 m^3/h, 1°C cooling means 3.4 $kWh_{cooling}$ (corresponding to 0.56 $kWh_{electric}$; chiller European seasonal energy efficiency ratio = 6) and 1°C heating means 3.4 $kWh_{thermal}$ (corresponding to 0.4 Nm3/h natural gas, heating system efficiency 85%).
- Example 4, using less severe internal thermo-hygrometric conditions: Considering that the internal hygrometric conditions depend on the cooling and dehumidification of the make-up air in summer and steam humidification in the winter, the calculation of the operating cost of the cleanroom with three different internal conditions is referred to the pretreatment of the make-up air.

CONCLUSION

High operating costs for a cleanroom are mainly due to the HVAC system. Most cleanrooms currently in operation were planned and built following design criteria that were defined some years ago and were consistent with the production and plant technologies available then.

Over the years, significant progress has been made in process technology. The pharma industry is increasingly moving toward single-use equipment, fitting, and tubing; functionally closed process steps that are isolated from the surrounding cleanroom air; and more efficient localized protections (isolation technology) for open processes. Better-performing garments have been developed and significantly reduce the emission of particles and MCPs. Operating procedures have also improved, simplifying the work of operators, increasing use of electronic batch records, implementing paperless documentation, and reducing the shedding of particles.

Consequently, some biopharmaceutical companies have updated their guidelines, reducing the minimum air changes to reflect these advances. With reduced air changes required in cleanrooms, companies can maintain compliant, controlled contamination environments while reducing energy consumption.

Table 4: Examples of energy savings.

	Cleanroom Indoor Temperature and Relative Humidity*	Annual Cost (Euros) of 1 m^3/h of make-up air treatment	Annual CO_2 (kg) per 1 m^3/h make-up air treatment
Case 1	Summer: 22°C, 50% Winter: 22°C, 40%	1.62	5.06
Case 2	Summer: 22°Cm, 55% Winter: 22°C, 35%	1.51	4.91
Case 3	Summer: 22°C, 60% Winter: 22°C, 30%	1.43	4.86

Assumptions:
- Costs are based on yearly outdoor condition for mid-Europe region.
- 180 g CO_2 per kWh due to natural gas consumption.
- 352 g CO_2 per kWh due to electrical energy consumption.

*Less-stringent indoor conditions can be applied once it has been verified there is no risk of discomfort to operators and no impact on production process.

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About the author

Emilio Moia is an Engineering Manager and subject matter expert in HVAC design and energy optimization with Jacobs' advanced facilities business. Emilio works with pharmaceutical companies to identify the design of HVAC systems that fit plant requirements, providing his knowledge and acumen based on more than 30 years' experience in HVAC design and engineering for aseptic production, isolation technology, HAPI plants, biotech plants, and laboratories. Working on world-class facilities, Emilio offers his expertise in the definition and development of solutions for key technical issues relating to the energy efficiency of the facilities and carbon footprint reduction. Emilio is a chartered engineer and holds a master's degree in mechanical engineering from Politecnico di Milano, Italy.

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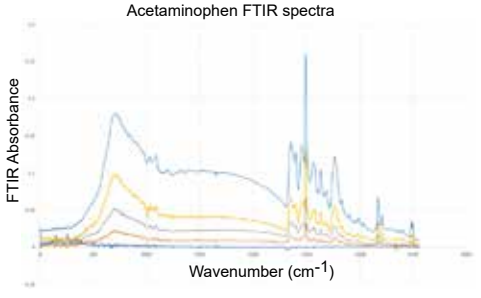

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TEMPERATURE AND HUMIDITY REQUIREMENTS in Pharmaceutical Facilities

By Nicholas R. Haycocks, Norman A. Goldschmidt, and Ulla Thomsen

Defining room temperature and humidity limits is a frequent topic of debate when designing and operating pharmaceutical and biotechnology facilities. What are appropriate alarm limits and acceptable durations for an alarm condition? Understanding the source of temperature and humidity requirements, and strategies for setting limits, can ensure both compliance and optimum use of energy. This article provides guidance on these topics, with supporting rationales.

Although temperature and humidity are both understood to be critical factors in the design and operation of compliant manufacturing facilities, regulations on these topics are surprisingly vague. In general, regulations suggest that temperature and humidity should be appropriate within manufacturing areas, with attention given to long-term storage areas, although needs are understood to be largely product specific. Tables 1 and 2 present key EU and US regulatory guidance from *EudraLex* [1, 2] and the US *Code of Federal Regulations* (CFR) [3], respectively.

CONSIDERATIONS WHEN SPECIFYING DESIGN RANGES

If there are no temperature or humidity limits for the product/process (which is often the case in closed processes with "internal" environmental controls), the temperature control of surrounding spaces defaults to that which is required for human comfort and to minimize shedding. An approach that ensures facility conditions are appropriate for the product and process, as well as for the gowning level of the workers, forms a reasonable basis for establishing the conditions for cGMP facilities.

Comfortable Conditions

Good engineering practice suggests specifying conditions that provide comfortable conditions for most workers. Factors to consider when defining comfortable conditions include:

Table 1: EU regulations related to temperature and humidity controls [1, 2].

Source	Regulatory Guidance
EudraLex Volume 4, Part 1, Chapter 3	3.3. Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment. 3.19. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.
EudraLex Volume 4, Annex 1	16. Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard. 73. Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.[a]

[a]Note that this guidance indicates that temperature may be governed by factors other than product or process requirements, such as the level of gowning.

Table 2: US regulations related to temperature and humidity controls [3].

CFR Section	Regulatory Guidance
211.42.3.10	Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures…Aseptic processing, which includes as appropriate…(ii) Temperature and humidity controls.
211.46b	Equipment for adequate control over air pressure, micro-organisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.
211.142	Warehousing procedures. Written procedures describing the warehousing of drug products shall be established and followed. (b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.

Figure 1: Seasonal comfort (temperature and RH). ©ASHRAE, www.ashrae.org. Used with permission from 2017 ANSI/ASHRAE Standard 55 [4].

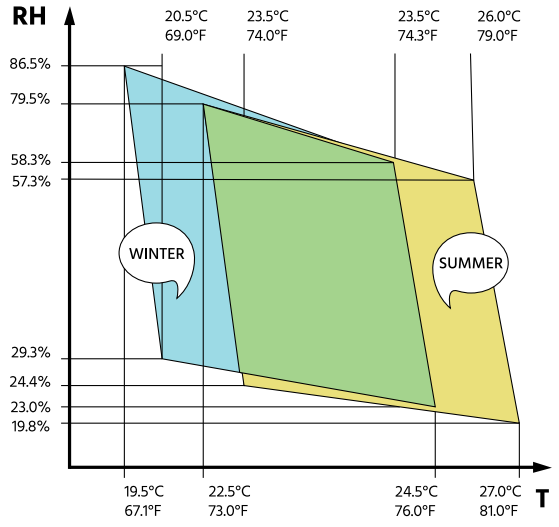
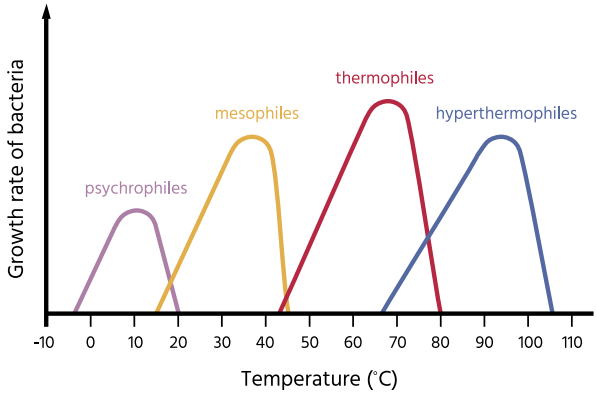


Figure 2: Microbial growth rate as a function of temperature. Notice that the curves are skewed toward the optimum temperature. The skewing of the growth curve is thought to reflect the rapid denaturation of proteins as the temperature rises past the optimum for growth of the microorganism. (Courtesy of OpenStax Microbiology.)



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- Metabolic rate (activity level)
- Amount of clothing
- Temperature
- Local airspeed
- Humidity
- Skin state (wetness)
- Individual preferences

There are several methods for defining the conditions that most people will find comfortable. For example, in the US, ANSI/ASHRAE Standard 55 *Thermal Environmental Conditions for Human Occupancy* [4] establishes a range of indoor conditions (temperature and relative humidity [RH]) intended to provide acceptable thermal comfort for building occupants (Figure 1). This American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) standard was first published in 1996 and has been regularly updated since 2004, with the most recent version published in 2017. The Chartered Institute of Building Services Engineers in the UK produces similar guidance [5].

The comfort levels indicated in Figure 1 assume the building occupant is wearing "street clothes" without overgarments. The addition of gowning would drive acceptable temperature and humidity levels down (in order to maintain a consistent RH). Common industry practice is to provide lower environmental temperatures as the level of gowning increases. We suggest that room temperatures for occupants wearing "street clothes" should have a setpoint around 22°C, whereas ISO 8 environments should have a setpoint around 20°C and ISO 7 environments a setpoint closer to 17°C–18°C.

These suggestions are based on the need for higher levels of gowning in more highly classified areas (Grade A or B [2], or ISO 5 or 7, in operation), which may include plant uniforms, coveralls, hoods, overboots, sleeves, and double gloves. In these situations, it is usual to set the lower end of temperature acceptance criteria quite low (e.g., 10°C). When designing internationally, it is important to also consider local customs and practices, as these may impact workers' comfort.

Microbial Growth

It is well known that temperature and humidity impact microbial growth and germination of spores (Figure 2) [6].

Temperature is a consideration for microbial growth: An increase in room temperature from 20°C to 25°C can roughly double the rate of bacterial multiplication. Mold propagation is more likely at warmer temperatures (up to about 35°C–40°C). Humidity also has an impact on the ability of the environment to support growth of any viable contaminants.

Water Activity

The ISPE *Good Practice Guide: Process Gases* [7] discusses water activity in relation to microbial and sporicidal growth. This guidance is based on USP<1112>: Application of Water Activity Determination to Nonsterile Pharmaceutical Products [8], which states:

> *Water activity, aW, is the ratio of vapor pressure of H_2O in product (P) to vapor pressure of pure H_2O (Po) at the same temperature. It is numerically equal to 1/100 of the relative humidity (RH) generated by the product in a closed system. RH can be calculated from direct measurements of partial vapor pressure or dew point or indirect measurement by sensors whose physical or electric characteristics are altered by the RH to which they are exposed.*

Figure 3: Water activity versus bacterial growth.

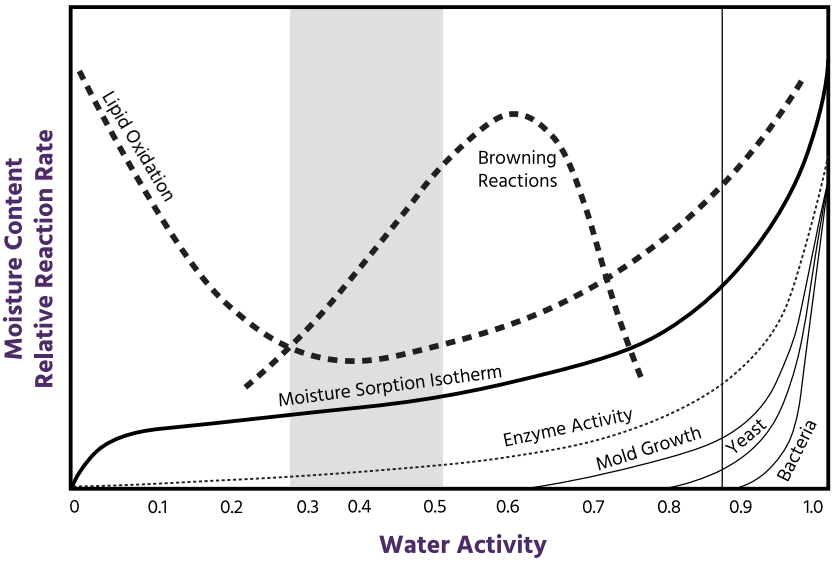
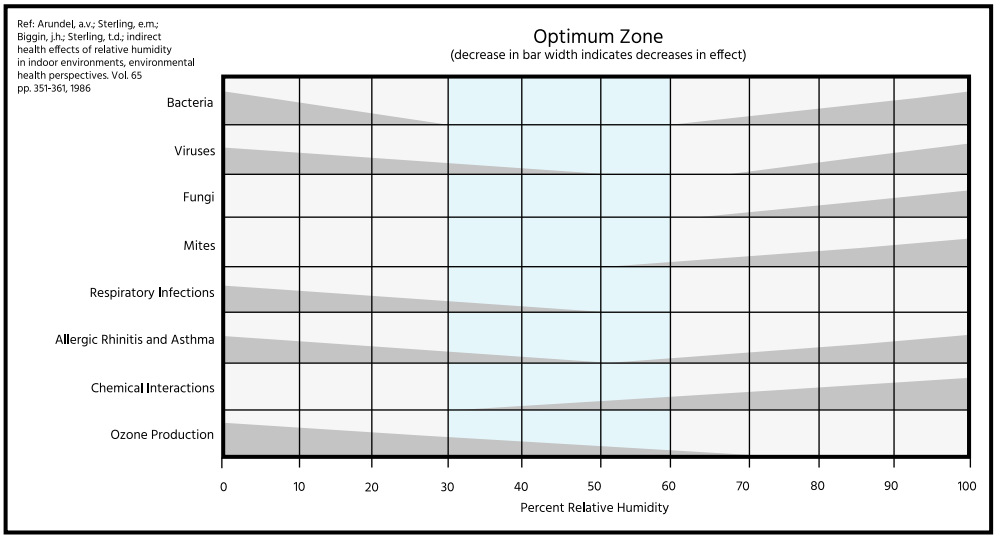


Figure 4: Environmental health and comfort. Reprinted from [9].



The relationship between aW and equilibrium relative humidity (ERH) is represented by the following equations:

$aW = P/Po$ and $ERH\ (\%) = aW \times 100$

Microbial growth and germination of spores are very unlikely in areas with an RH below 60% (see Figure 3). Figure 4 shows the relationship between environmental health and comfort [9].

Vegetative cells would normally be carried on particles, such as skin flakes, and are fragile. Mold spores and bacterial spores are much hardier; they can exist as individual spores and then grow when they find a suitable growth environment. They can enter a facility on people or materials.

Bacterial spores are typically 1–2 µm in length and 0.5–1.0 µm in diameter. Mold spores are typically larger, between 4 and 20 microns [10]. Mycotoxins are toxins produced by some species of mold (secondary metabolites) and are as small as 0.1 µm. *Aspergillus* species and *Penicillium* species mold spores range from 1 to 8 µm.

Keep in mind that although high-efficiency particulate air (HEPA) and ultra-low particulate air (ULPA) filters are highly effective against microbial contamination, they are not truly

absolute filters. If the microbial load upstream of these filters is high enough, some penetration is possible.

Storage Spaces

According to USP<659>: Packaging and Storage Requirements [11], temperature and humidity conditions for the acceptable storage of materials are divided into freezer, refrigerator, cold, cool, controlled room temperature (CRT), warm, and excessive heat. With regard to temperature and storage, USP<659> further states:

> *Specific directions are stated in some monographs with respect to storage conditions (e.g., the temperature or humidity) at which an article must be stored and shipped. Such directions apply except where the label on the article has different storage conditions that are based on stability studies. Where no specific directions or limitations are provided in the article's labelling, articles must be protected from moisture, freezing, and excessive heat, and, where necessary, from light during shipping and distribution. Drug substances are exempt from this standard.*

Based on this guidance, we understand that the "ambient storage" conditions used for ambient storage warehouses should be aligned with the USP CRT guidance, which states, "Storage spaces classified as 'ambient' are therefore expected to be not more than 25°C on average with a 15–30°C acceptance range" [11].

USP<659> defines CRT as follows [11]:

> *The temperature maintained thermostatically that encompasses the usual and customary working environment of 20°–25° (68°–77°F). The following conditions also apply. Mean kinetic temperature not to exceed 25°. Excursions between 15° and 30° (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses, and during shipping are allowed. Provided the mean kinetic temperature does not exceed 25°, transient spikes up to 40° are permitted as long as they do not exceed 24 h. Spikes above 40° may be permitted only if the manufacturer so instructs.*
>
> *Articles may be labeled for storage at "controlled room temperature" or at "20°–25°", or other wording based on the same mean kinetic temperature....*
>
> *An article for which storage at Controlled room temperature is directed may, alternatively, be stored and shipped in a cool place or refrigerated, unless otherwise specified in the individual monograph or on the label.*

Storage spaces classified as "ambient" are therefore expected to be not more than 25°C on average, with a 15°C–30°C acceptance range.

TEMPERATURE RANGE RECOMMENDATIONS

CRT Storage Spaces

The US Pharmacopeia uses the mean kinetic temperature (MKT, "the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures") in its CRT guidance [11]. However, it is common practice to set "engineering" (alert) alarms for CRT storage spaces at 20°C and 25°C with "quality" (action) alarms for these spaces at 15°C and 30°C. Keep in mind that the wider the used operational range is, the lower the energy consumption for heating, cooling, humidification, and dehumidification will be.

Table 3: Suggested temperature ranges for facility space design conditions.[a]

Space	Lower Limit, °C	Operating Range, °C	Upper Limit, °C
Plant utilities room	5	15–27	90
Clean utilities (technical space)	5	20–25	65
Raw materials warehouse (ambient)	10	15–30	35
Raw materials warehouse	15	20–25	30
CNC	15	20–24	30
CNC+/Grade D	15	18–22	30
ISO 8/Grade C	15	18–22	30
ISO 7/Grade B	14	17–20	30
ISO 5/Grade A	14	17–20	30
Finished goods (refrigerated)	2	3–7	8
Finished goods (CRT)	15	20–25	30

[a]Alert alarms should be set close to the operating limits to provide early notification of a potential issue; the limits given are proposed for initial settings used while gathering operational data.

Manufacturing Areas

Temperature is generally controlled in the range of 15°C–25°C for manufacturing and storage facilities, except where a process or product requires more stringent control. In the case of human comfort, the acceptable range may be broad (e.g., 20°C ± 5°C). However, general practice is to maintain control within a narrower range, such as ±2°C–3°C, and, in some cases (for example, for older control systems that may not be as responsive for temperature control), it is advisable to use a range that allows the temperature to heat up to a maximum temperature and cool down to a minimum temperature. It is also a good practice in terms of minimizing energy consumption to shift the setpoint seasonally to accommodate how workers' perceptions of comfort shift with seasonal changes (see Figure 1).

Where temperature limits are defined by process or product requirements, industry best practice is to ensure that the alert range accounts for instrument error. The National Environmental Balancing Board suggests that instrument error should be within 1.0% of reading [12]. This should be considered when setting alarm set points.

Ideally, alarm levels are determined after observing the variability of specific systems. Typically, a short alarm time delay is

incorporated to avoid any nuisance alarms set off by short-term fluctuations that may be caused by an influx of air from an adjacent area that is operating at different conditions, or any signal noise.

DESIGN CONDITIONS

It is common for design conditions to be largely based around comfort factors (except where special conditions outside of these are needed for products or processes). Therefore, short-term excursions are often not a quality concern. Table 3 summarizes suggested temperature ranges to use as design conditions for various spaces, including controlled not classified (CNC) spaces. CNC spaces are [13]:

> *Areas where HVAC systems are specifically designed to reduce airborne contaminants below the level of the ambient environment and both temperature and RH are controlled more tightly than in the ambient environment. Claims for environmental control in these areas are related to the design of the system; installation qualification is common. No claim is made or qualified for the specific control of particulate. Typical systems will have heating, cooling, and filtration meeting minimum efficiency reporting values of 13 (F7) or better. These areas are sometimes referred to as "pharmaceutical" or "clean" areas within pharmaceutical facilities.*

The temperature values presented are lower than suggested in the ISPE *Baseline Guide, Volume 6: Biopharmaceutical Manufacturing Facilities*, second edition [14], based on our experience of operator comfort in the gowning associated with each classification of space.

HUMIDITY RANGE RECOMMENDATIONS

Design and Operating Ranges

As with temperature, regulatory guidance suggests that humidity levels should be appropriate for the product and process as well as for operator comfort and to limit shedding and sweating. Therefore, if humidity does not affect product and process, RH is commonly maintained within a band, at levels less than 60% (see Figure 4), with the lower RH limit defined by local custom and practice. Controlling the lower range of humidity is not generally important to address microorganism-related concerns, but it may be important to manage static electricity, human comfort, and shedding.

The acceptance range can be broad: It is not uncommon to see humidity acceptance ranges between 30% and 60% RH, as suggested by ASHRAE [4] (see Figure 4) and the ISPE *Baseline Guide* [14]. Some companies successfully extend the acceptance range from 20% to 70% RH, based on the location (with consideration of local flora and fauna, cleaning methods, etc.).

To achieve the acceptance range, general practice is to maintain setpoints near 25%–55% RH and allow the system to respond if RH levels exceed those limits. These limits may be adjusted seasonally to accommodate how workers' perceptions of comfort shift with seasonal changes (see Figure 1).

Table 4: Suggested RH ranges for facility space design conditions.[a]

Space	Lower Limit, % RH	Operating Range, % RH	Upper Limit, % RH
Plant utilities room	N/A	≤80	90
Clean utilities (technical space)	N/A	≤60	65[b]
Raw materials warehouse (ambient)	N/A	20–80	90
Raw materials warehouse (controlled)	N/A	30–60	65[b]
CNC	25	30–60	65[b]
CNC+/Grade D	25	30-60	65[b]
ISO 8/Grade C	25	30–60	65[b]
ISO 7/Grade B	25	30–60	65[b]
ISO 5/Grade A	25	30–60	65[b]
Finished goods (refrigerated)	N/A	20–80	90
Finished goods (CRT)	N/A	20–75	80
Dry storage (CRT)	N/A	30–40	45

[a]Broader operating ranges with higher upper limits have been successfully used with appropriate qualification and monitoring of data regarding the impact of RH on local microbial growth. Alert alarms should be set close to the operating limits to provide early notification of a potential issue; the limits given in the table are proposed for initial settings used while gathering operational data. N/A = not applicable.
[b]Upper limits may be raised with proper qualification and data.

Storage Spaces

According to the US Pharmacopeia, humidity conditions for the acceptable storage of materials are divided into "dry" and unspecified conditions. The USP<659> [11] definition of a "dry" place is as follows:

> *A place that does not exceed 40% average relative humidity at 20° (68°F) or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place. Determination is based on NLT [not less than] 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to 45% relative humidity provided that the average value does not exceed 40% relative humidity. Storage in a Container validated to protect the article from moisture vapor, including storage in bulk, is considered a Dry place.*

Humidity Alarm Set Points and Delay Times

It should be noted that, at a constant absolute humidity, RH increases as temperature decreases, making low-temperature environments more susceptible to exceeding RH limits. If moisture is a product or process requirement, it may be more efficient to control moisture to an absolute level (grams of water per kilogram of air) to remove the effect of temperature; often the humidity issue is due to the partial vapor pressure.

High RH levels can initiate a biological process. Because the biological processes of mold spore germination or bacterial reproduction have time constants of their own, it is normal to accept a delay in the initiation of RH alarms that is shorter than the time required for the biological process to move to completion, and longer than the time required for typical wet tasks, like cleaning. In the case of common mold types on building materials, the germination period often exceeds 24 hours. For this reason, although the speed of germination will likely increase with increases in RH, there is a period during which any RH level, even close to 100%, may be tolerated for short times. Common wet cleaning processes rely on this principle, as the water that is applied to a surface during cleaning will not promote mold propagation so long as it evaporates within a reasonable period. However, if an area is allowed to stay at a high humidity level for an extended period (e.g., in a shower), microorganisms can propagate.

Alarm set points should consider instrument error. The National Environmental Balancing Board suggests that verification instrument error should be within 2% of the reading range [12]. Coupled with the measurement instrument error, this suggests that alert ranges should not normally be less than ±5%.

For these reasons, it is suggested that alarms for RH incorporate delays as needed to accommodate excursions caused by normal operation (doors opening, cleaning, etc.). A period of 1–4 hours is common for an alarm delay, given that this period is usually enough to complete cleaning but does not provide time for significant expansion of microbial colonies or germination of mold spores. Delays of up to 24 hours may be justified based on the time required for microbial contaminants to propagate in a region.

For existing facilities that are not designed to control RH to less than 65%, an alarm delay of 12 hours could be used for RH above 70%, prior to cessation of operations. Low-level alarm set points would be based on local practices.

Note that in all cases, vented steam or hot water vapor from component washing and equipment cleaning/sanitization should have a local exhaust.

Design Conditions

It is common for design conditions to be based around a combination of comfort factors and upper limits to inhibit microbial growth (except in situations where special conditions are needed for products or processes, such as effervescent tablet manufacturing). Again, short-term excursions are often not a quality concern. Table 4 summarizes suggested RH ranges to use as design conditions for various spaces.

PRACTICAL ADVICE FOR CONTROLLING MOLD

Fungal spores are always present. If the prevailing conditions do not encourage growth, there are no problems; however, many facilities experience mold issues. According to the Centers for Disease Control and Prevention, when buildings are wet for more than 48 hours (e.g., following a flood or hurricane), "visible and extensive mold growth" is likely [15].

Mold problems may be identified by higher particle counts, followed by visible signs of contamination, or through environmental monitoring. According to an industry specialist in restoration, "under ideal conditions (optimal temperature and level of humidity), it takes 24 to 48 hours for mold to germinate and grow. Typically, the spores begin to colonize in 3 to 12 days and become visible in about 18–21 days" [16].

For mold spores to germinate and proliferate, conditions must be conducive to growth. For example, a pipe leak could allow water to enter drywall (gypsum board) or cleanroom panels, or water used during cleaning could penetrate a joint to sit on timber. In a cold room or freezer, mold may grow when high humidity is caused by an internal air leak around a utility penetration, leading to internal condensation.

If mold is suspected or confirmed, the following points may be worthy of investigation:

- Residual moisture in ductwork: Common sources of moisture include damaged vapor barriers on ductwork insultation or the humidification system not draining fully.
- Residual moisture in and around air-handling units (AHUs): poorly draining condensate pans under cooling coils, poor sealing of insulated AHU panels, and air leakage from the negative pressure section can allow moisture and condensation.
- High room-humidity levels: Consider reducing the RH level to approximately 55%.
- Leakage of contaminated air: Determine whether airflow direction changed, even for a short time period. This issue can be caused by poor sealing between cleanroom panels. In one case, the process area HVAC was turned off to ensure there was adequate contact time for the sanitizing material, and this allowed contaminated air to leak in due to "loose" mastic seals between panes; the adjacent service area was at a slightly higher pressure, and there was a drain by the poor joint in the service area.
- Sanitization and cleaning practices: Are all cleaning materials, including mops, sanitized? Are the cleaning or sanitizing materials a potential source of contamination?
- Spore transfer from another area: For example, contamination could be due to an instrument tech wheeling a cart from one building to another, with inadequate wheel cleaning (dedicated carts are preferable). A worker's shoes or clothing could also carry contaminants from one region to another.
- The adequacy of sealed cleanroom finishes: In one instance, mold was found on plywood blocking behind the wall finish, where the seal was inadequate. In another case, mold was found in a hole in the top of a door, which turned out to be stainless cladding over wood.
- Sources of condensation between walls due to temperature gradients in adjacent rooms: For example, if a wall in a cold room wall sweats, investigate whether the damp-proof membrane is in the right location.
- Equipment operating below the dewpoint of the conditioned space: This can result in the formation of condensation.

Prompt remediation is required when mold is discovered. For porous materials, cleaning or sanitizing is difficult, and replacing contaminated materials is advised. If drywall is contaminated, the only solution is demolition and replacement. For nonporous materials, cleaning and sanitizing can be effective once the source of moisture is removed.

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SAFEGUARDING VIAL CONTAINER CLOSURE INTEGRITY: A Systematic Approach

By Qingyu Zeng, PhD

Any systematic pharmaceutical engineering approach for ensuring vial container closure system (CCS) performance must include choosing qualified CCS components, the proper pharmaceutical process setup, and applicable testing methods. Container closure integrity (CCI) is an essential part of CCS performance. A holistic strategy is needed to qualify CCS performance under the required temperature conditions during the entire product shelf life. To minimize potential safety risks and ensure the best CCS performance, the strategy must balance and optimize many critical variables through a data-driven approach to informed decision-making.

Primary packaging plays a critical role in maintaining drug quality and full regulatory compliance throughout the product's shelf life. A vial CCS for pharmaceutical, biological, cell, and gene therapies must maintain CCI to ensure that the drug products remain stable and free of contamination from microbial ingress. Pharmaceutical engineering for CCS must include CCS component qualification, a pharmaceutical process setup for assembling the CCS, storing and shipping the pharmaceutical product through various conditions, and proper evaluation of the CCS to ensure its CCI throughout the entire sealed product shelf life.

CCS REGULATORY COMPLIANCE

Appropriate CCS performance is mandatory before pharmaceutical products are made available for human use. Among the key guidance publications for CCS qualification are US Pharmacopeia (USP) Chapter <1207> [1]; US FDA guidance [2]; EudraLex, Volume 4, Annex 1 [3]; and ICH Q5C [4]. These guidance documents include general guidelines and various testing methods.

To ensure patient safety and meet regulatory requirements for CCS, a number of factors must be addressed, including risks associated with gas and moisture ingress, changes in vacuum pressure, leakage, capping, sealing, visual inspection acceptance, and temperature cycling.

Gas and Moisture Ingress

Pharmaceutical products, including cell and gene therapy products and short-life biologics, may contain molecular structures or chemical function groups and fully functional cells that are sensitive to oxidization and pH value changes. Oxygen may cause oxidation in the product. Carbon dioxide (such as the dry ice used for storage and shipping) can be easily dissolved in solution and become carbonic acid, which can lower the solution's pH. Some drugs can be sensitive to moisture, which causes drug degradation. Ingress of gases, such as oxygen or carbon dioxide, and moisture must be controlled according to drug sensitivity and specific product requirements. Additional protection can be achieved by filling the CCS headspace with an inert gas, such as nitrogen.

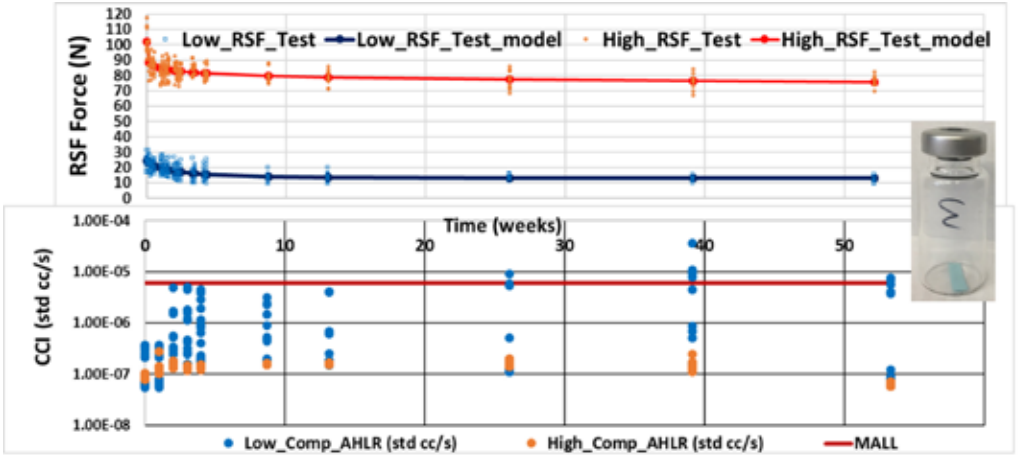
Changes in Vacuum Pressure

The CCS may have to go through the lyophilization process and may need to maintain a specific internal vacuum pressure level at cold temperatures over the product shelf life. This vacuum pressure level may be intentionally designed for the purpose of drawing a controlled liquid through a needle inserted into the vial CCS at the moment of patient administration. If a vacuum is specified to aid in the reconstitution of a lyophilized product, the loss of that vacuum or a change in vacuum pressure could lead to incomplete reconstitution or extraction of the drug product, thereby delivering an inaccurate dose to the patient.

Leakage Control

Most pharmaceutical package types may display extremely low leakage flow through the gap that exists even between well-fitted closures [1]. From the practical view of pharmaceutical engineering, a vial CCS package should not permit leakage beyond the maximum allowable leakage limit (MALL) [1] to maintain acceptable drug product sterility and stability. This limit is based on the

Figure 1: RSF and helium leak testing data for vial CCS using a 20 mm butyl elastomer stopper and a 10 mL glass vial fully filled with helium at ambient pressure, tested at ambient temperature through a vacuum chamber [8, 9].



actual drug packaging system and its specific requirements. To satisfy CCI requirements, companies must use a systematic approach to minimize leakage that includes choosing an appropriate CCS, qualifying compatible CCS components, setting up a robust pharmaceutical process for assembling the CCS, maintaining proper storage and shipping conditions to minimize the potential impact of cold temperature and duration, and establishing suitable testing methods for quantifying and ensuring CCS quality during the sealed product shelf life. Prior to use, all individual components must be protected from improper storage and shipping conditions that could damage the parts.

Capping, Sealing, and Temperature Cycling

A typical vial CCS configuration has three major components: a vial, an elastomer stopper, and an aluminum seal with or without a flip-off button [5]. Among these CCS components, the elastomer stopper plays a critical role by deforming to seal the vial-stopper interface area either temporarily or permanently. From a pharmaceutical engineering point of view, the vial CCS packaging includes both the selection of CCS components and the capping process setup for delivering CCS performance. Typically, the CCS assembly is capped at room temperature. For a lyophilized product, the vial may be vacuumed to a pressure below the ambient pressure and may be filled with an inert gas (e.g., nitrogen) before being stoppered and capped.

The capped CCS assembly may have to undergo required cold temperature cycles for processing, storage, and shipping. For example, it is common to store and ship some biological and cell and gene therapy products in the frozen state (e.g., in dry ice at –80°C or at cryogenic temperature below –150°C). These low-temperature cycles may have an adverse impact on CCI performance [6, 7] and the sealing performance of CCSs in cold temperature conditions is important. Any CCI breach could potentially lead to the ingress of oxygen, carbon dioxide, moisture, or microorganisms and, consequently, could risk the drug product integrity and stability depending on drug molecular structure sensitivity, potentially jeopardizing patient safety.

Because any CCI breach may risk patient health, the components—elastomer stopper, vial, and aluminum seal—together with the capping process, must be properly selected, set up, and controlled to ensure acceptable CCI performance under the required temperature conditions during the entire product shelf life. CCS qualification should occur with the desired component options or platforms that will be employed for the drug's final presentation. It is necessary to look at the CCS package in its entirety.

Residual Seal Force (RSF)

The CCS components come together as the primary packaging system that provides a barrier to protect a sterile drug product from product loss and from microbial or environmental contamination. The elastomer stopper provides a significant amount of this protection, and factors affecting its performance are discussed here. One of the benefits of using an elastomer stopper is its ability to deform and form a sealed interface with another material, such as a glass or polymer vial. This ability can be adversely affected if the composition of the elastomer itself or the surface of the component is not pliable. To ensure acceptable CCI, a vial CCS must maintain adequate residual seal force (RSF), which is the force that an elastomer stopper flange exerts against the vial flange surface in a capped vial CCS. RSF is included in USP Chapter <1207> as a seal quality test for parenteral vials [1]. The RSF within a CCS is inherently time-dependent, decaying exponentially over time and eventually leveling off owing to elastomer stopper compression stress relaxation (CSR) [8, 9]. This is shown in the top graph of Figure 1, in which testing and modeling data are used to present RSF as a function of time. To ensure sufficient RSF throughout the entire product shelf life, it is important to use a qualified stopper together with a proper capping process setup.

Typically, stopper materials are made of elastomer compounds primarily composed of polymers and additives. These material

Because any CCI breach may risk patient health, the components and capping process must be properly selected, set up, and controlled.

ingredients are specifically chosen and engineered both for manufacturing processing purposes and to satisfy the requirements for end-product application performance. Elastomer polymer molecule structures may be linear, branched, cross linked, or networked, all of which affect the chemical, physical, and mechanical properties of the elastomer stopper [10, 11], resulting in both elastic and viscous resistance to compression [12, 13].

Compression Stress Relaxation

In effect, elastomer stoppers can partially retain the recoverable (elastic) strain energy, but they can also partially dissipate (viscous) energy if stopper compression is maintained after capping. Therefore, under constant compression, elastomer stoppers undergo compression stress relaxation (CSR). By following the Maxwell-Wiechert model of polymer structures and properties, a physical and mathematical model can be developed to describe elastomer CSR under compression [12, 13].

The top graph in Figure 1 provides an example from a case study to show RSF relaxation decay in testing and modeling data [8, 9]. Figure 1 also demonstrates the relationship between RSF and the results of CCI testing for helium leak up to one year after sealing. It clearly shows that RSF inherently undergoes time-dependent CSR owing to the viscoelastic nature of the elastomer stopper materials. Typically, a high stopper compression percentage leads to high RSF. The degree of stopper CSR could affect the ultimate sealing capability of the CCS to meet CCI requirements throughout the entire sealed drug shelf life. In general, as shown in Figure 1, a high RSF leads to relatively low helium leakage results, with tight statistical spreads for good CCI performance, whereas low RSF results are associated with poor CCI performance, causing relatively high helium leakage results, and large statistical spreads, increasing the risk of failing the maximum MALL.

RSF relaxes over time because of the viscoelastic characteristic nature of the elastomer stopper materials. The magnitude and rate of RSF decay depend on the elastomer polymer's molecular structure, formulation, and properties; the CCS dimensions (stopper, vial, and aluminum seal); and the capping process setup. In fact, RSF decay can be engineered to a certain degree through the design of the elastomer molecule structure and by modifying the material properties for optimal CCI. The resultant RSF relaxation decay has an impact on whether the CCS can successfully maintain adequate CCI throughout the entire sealed drug product shelf life. To ensure acceptable CCI, proper stopper compression must be imposed by the capping process for maintaining acceptable RSF during the product shelf life.

SEALING PERFORMANCE AT COLD TEMPERATURE

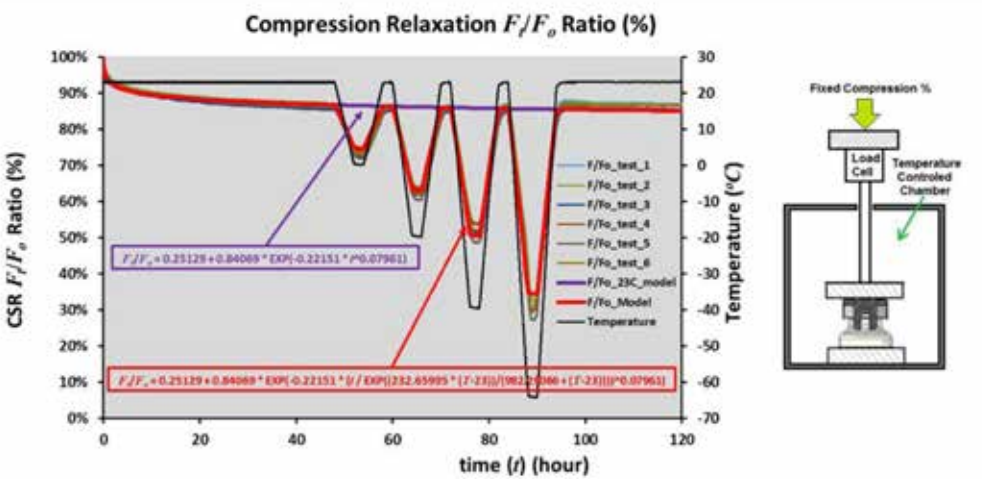
CCI should be considered over the drug product's shelf life, including when assessing transportation and storage conditions of the vial CCS packaging system. CCI must be stable under the multitude of potential circumstances that a vial product might encounter over its shelf life. In cold temperature applications, the CCS is typically assembled during a capping process at room temperature with the intent of obtaining sufficient RSF for acceptable CCI at cold temperatures.

The assembled CCS may need to withstand cold temperature conditions, per the requirements of drug processing or drug storage as well as shipping, and is typically then returned to room temperature for dosage injection. CCI may perform adequately at room temperature but be at risk at cold temperatures. For cold chain management, it is imperative to fully understand sealing performance changes related to time-temperature transitions and the subsequent impact of such changes on CCI performance.

The sealing properties of the elastomer stopper are highly dependent on temperature, which affects the mobility of the elastomer molecules and leads to the temperature-dependent nature of sealing force relaxation [12–14]. Fundamentally, the sealing force is dependent on both time and temperature, and these two factors are coupled together. The principle of time-temperature superposition for viscoelastic elastomer stoppers [15, 16] is applicable. This means that the stopper sealing force at one temperature can be related to the force at another temperature by a change in the timescale only (i.e., a change in temperature is equivalent to a change in the stress relaxation rate).

ISO 11346 [17] describes the principle and methods for time-temperature superposition used both by industry and the research community. These methods are commonly used for time-temperature superposition calculations of elastomer stress relaxation. The time-temperature superposition for elastomer stopper materials may not be valid for the same elastomer material below its glass transition temperature because the viscoelastic elastomer material will be vitrificated, owing to the freezing of the elastomer molecule segment motion, whereby it will become a rigid solid material with very different properties in a physical sense. However, the viscoelastic elastomer stopper material has the memory capability to resume its time-temperature superposition track once the temperature rises above its glass transition

Figure 2: CSR testing and modeling for 20 mm butyl stoppers through different temperature cycles, both testing (six samples) and modeling data (red legend) [6]. Reprinted by permission of the author.



temperature again. Subsequently, its elastomer molecule segment motion is resumed as well [12–14].

Figure 2 shows a case study [6] of 20 mm butyl stopper CSR testing per ISO 3384-1 [14], with stopper compression fixed at 25% and testing temperatures programmed to include some fluctuating temperature cycles in real time, oscillating between 23°C and -65°C and to the 23°C reference temperature baseline.

As shown in Figure 2, the dimensionless compression force ratio F_t/F_0 is presented as a function of time, where F_t is the actual compression force measured at time *t* and F_0 is specified as an initial compression force at time zero. The F_t/F_0 ratio represents the compression relaxation property of the elastomer stopper material. It is important to ensure an acceptable F_t/F_0 ratio for sufficient RSF throughout the entire product shelf life using a qualified stopper together with the proper capping process setup.

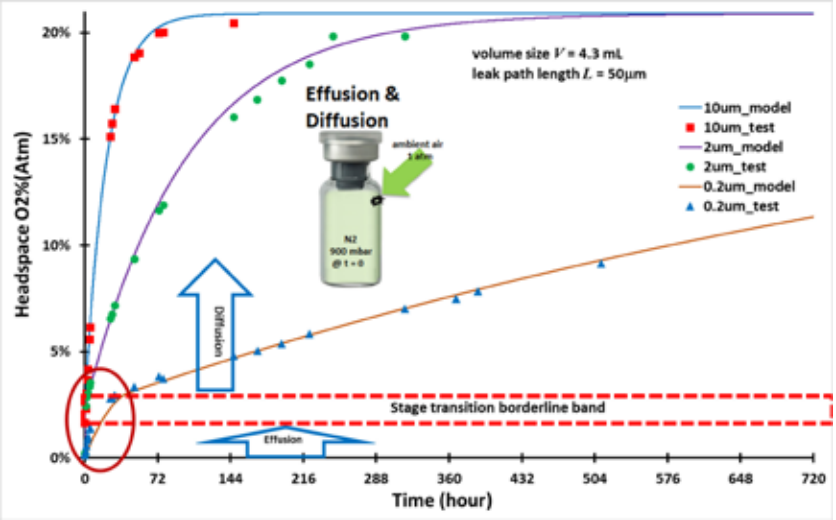
CCI risk at cold temperatures has been a potential issue for the drug industry. In general, material temperature is a function of the average molecular kinetic energy of the elastomer stopper material [10–13]. When the elastomer stopper material is heated, the kinetic energy of its molecules increases. Thus, the elastomer molecules begin vibrating and moving more and usually maintain a greater average separation owing to thermal expansion. This temporary elastomer material expansion is reversible once the temperature decreases and causes shrinkage. Elastomer shrinkage may cause CCI failure.

When testing temperatures are between 23°C and –65°C, the stopper compression sealing force relaxation ratio F_t/F_0 decreases as the temperature decreases and increases as the temperature increases. The decrease in the ratio, along with the fall in temperature, is mainly caused by the temporary shrinkage of the elastomer stopper at cold temperatures. This cold shrinkage could cause a gap or leak path between stopper and vial [18]. After going through temperature cycling, the compression relaxation ratio F_t/F_0 has the memory capability to return from -65°C to its relaxation track at the 23°C temperature baseline, as shown in Figure 2. Apparently, the elastomer stopper regains its sealing force and reseals the CCS after rewarming to ambient temperature. However, it must be emphasized that if all the CCI testing is done at room temperature before and after the cooling cycle, some CCI testing methods may not be able to capture the possible leakage damage already done to the drug during the cold temperature cycle.

The results in Figure 2 provide insight into the problem of CCI performance risk at cold temperatures, which has been experienced as an issue in drug industry. In general, different elastomers will follow behavior similar to that demonstrated in Figure 2. This similar behavior needs to be quantitatively verified and validated to ensure CCS performance for applications. The original modeling equation (in red font) has both time *t* and temperature *T* as variables for the time-temperature transition, and the modeling data match relatively well with the testing results of the time-temperature transition. This elastomer stopper material has a glass transition temperature T_g of –61.12°C, tested per the ASTM D7426 standard test method [19]. The time-temperature superposition modeling evaluation is applicable to the elastomer stopper material in its viscoelastic status.

Figure 2 for this particular elastomer stopper clearly demonstrates that cold temperature reductions in the sealing force are much more significant than time-dependent relaxation and have a more noticeably adverse impact on sealing performance. Therefore, for proper risk management, it is important to understand the CCI of the CCS throughout its entire supply chain. This aspect of CCI, especially under extreme conditions, must be considered because some materials or CCS packaging systems may not be optimal under certain environmental conditions. Cold temperature conditions, especially below –60°C, are likely close to or below the glass transition temperature of a butyl elastomer stopper formulation. At this point, the stopper loses its viscoelastic properties and becomes glass-like in nature. Under such temperature

Figure 3: Headspace oxygen percentage within CCS for two-stage transition of effusion and diffusion of sealed 4.3 mL vial with different defect sizes. Red circle area is for first stage of effusion-in before transition to second stage of diffusion [20, 21]. Reprinted by permission of the author.



extremes, materials can shrink or contract, thus creating a potential leakage path in the CCS and consequently a greater risk to CCI at cold temperatures.

CCI PERFORMANCE EVALUATION

CCS performance must be qualified for acceptable CCI. CCI is associated with the size of the leak path of the CCS. Figure 3 shows CCI modeling case study data of headspace of oxygen ingress through different leakage defect sizes [20] together with testing results [21]. For this case study, all three vials were subjected to the same conditions —the same 4.7 mL vial volume with 50 mm defect path length but different leak path diameters (d = 10 mm, 2 mm, and 0.2 mm, respectively); lyophilized, filled with 100% nitrogen gas, and evacuated to end pressure at 900 mbar—before being stoppered and capped tightly at time zero. The ambient air pressure is at 1 atm (1,000 mbar). This is a case of effusion-in. The term "effusion" is generally used in the parenteral packaging industry for gas leakage transmission, including concurrent diffusion and mass/volumetric flow into or from the vial. The diffusion is driven by the gas concentration differential. The mass/volumetric flow is driven by the total pressure differential, and oxygen ingress into a vial through a leak path can be calculated. Figure 3 shows the modeling results [20] and testing results [21] of headspace oxygen percentage over time.

Two stages of effusion and diffusion, respectively, through a seamless transition in real time are shown in Figure 3:

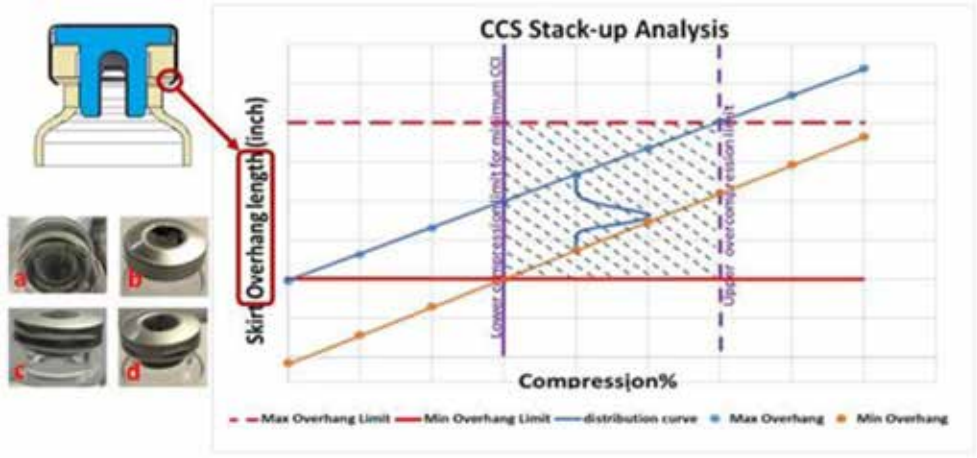
1. The first stage started with effusion-in and concurrently included both diffusion and mass/volumetric flow into the vials at time zero, with a total pressure differential of 100 mbar (1,000 mbar – 900 mbar = 100 mbar). This effusion-in stage ended once the total pressure differential fully dissipated and reached pressure equilibrium with no more mass/volumetric flow.
2. However, the inside of the vial is still oxygen deficient at the end of the first effusion-in stage because of the prior presence of nitrogen. The second stage immediately and seamlessly started as oxygen diffusion continued from the first stage into the vial without mass/volumetric flow in the second stage, eventually reaching a headspace oxygen pressure of 20.9% atm and equilibrium with the oxygen percentage in ambient pressure.

The modeling data accurately capture the stage transition points from the first effusion-in stage to the second diffusion stage, as highlighted by the red circle area in Figure 3. The oxygen percentage at the stage transition point differed from one leak path diameter to another. The timing of the total pressure equilibrium and its corresponding oxygen percentage depends on the defect diameter: about 8.9 seconds and 2.29% oxygen (atm) for a 10 mm diameter; about 8.3 minutes and 2.37% oxygen (atm) for a 2 mm diameter; and about 43.82 hours and 3.07% oxygen (atm) for a 0.2 mm diameter; all corresponding to the stage transition borderline band in Figure 3.

Clearly, when the leak diameter is bigger, the time to total pressure equilibrium is shorter, and the oxygen percentage (atm) is slightly lower when the end of the first stage is reached, owing to the predominance of quick mass/volumetric flow through the leak path, with little oxygen diffusion taking place simultaneously in the first stage. For a smaller leak diameter, it takes longer to reach the total pressure equilibrium, with a slightly greater oxygen percentage (atm) at the end of the first stage because more oxygen diffusion occurs simultaneously in that stage. It is clear that the size of a leak path has an impact on CCI. Modeling calculations can help provide quick screening evaluations in many cases when the testing method is either too limited or too costly [20].

Several CCI testing methods are commonly used in the pharmaceutical industry to quantify the magnitude of CCS leakage

Figure 4: Rejectable visible defects and diagram of a balanced CCS performance window to avoid defects [8, 22]. Photos: (a) Seal skirt wrinkling under the vial flange, (b) stopper dimpling, (c) seal side buckling, and (d) a combination of these defects. In the diagram, the blue line represents the maximum overhang length data points at discrete compression percentage points, and the yellow line is for the corresponding minimum overhang length data points. Reprinted by permission of the author.



for regulatory compliance (recalling that no CCS should permit leakage beyond the MALL). CCI testing methods can be deterministic or probabilistic: deterministic methods include helium leak testing, high voltage leak detection, laser headspace analysis, mass extraction, and pressure and vacuum decay methods; probabilistic methods include bubble leak and blue dye tests. With deterministic methods, the measurement of leak detection is based on physicochemical technologies that are readily controlled and monitored, yielding objective quantitative data. For this reason, the pharmaceutical industry has increased efforts to introduce and develop deterministic leak test methods for CCI testing.

However, any type of testing technique may have limitations based on many factors, including:

- A specific testing setup under highly specific testing conditions
- Destructive methods that do not occur under real-world conditions
- The inability with destructive methods to iterate testing on the same sample to identify trends
- Lengthy testing times for trending results from slow leakage
- Issues with representative sampling
- The resulting inability to reproduce and predict results for various real-world applications

Many aspects must be considered in a holistic CCI testing approach. There is no universally accepted CCI testing method, and each testing method and principle has merits and shortcomings. It is important to understand the science behind why a CCI testing method is chosen to ensure integrity, especially because there is a direct correlation between CCI and patient safety. The CCS package must be validated to ensure CCI can be maintained throughout the entire drug product shelf life.

OPTIMAL CCS PERFORMANCE

The quality of the final vial CCS package is determined by both the CCS components (vial, elastomer stopper, and aluminum seal) and the capping process. Empirical experience indicates that unexpected failure, manifesting as CCI failure, visual defects, or incomplete sealing, can occur over time. Therefore, choosing the appropriate elastomer stopper, vial, and aluminum seal, together with a capping and sealing process optimized around those components, is essential to ensuring reliable CCI and optimal CCS performance.

Engineering drawings can specify a range of dimensions for CCS components. Due to variations in manufacturing, each component of a CCS is a statistical variable. It is important to understand the statistical variations of the components, especially when limited information is available on compatibility or when multiple suppliers are utilized. Because of these variations, it is difficult to assess the likelihood of successful assembly, capping, and sealing for a given vial CCS when setting up a pharmaceutical capping process. In general, a capping process must be set up with proper stopper compression to ensure the RSF is sufficient at both time zero and throughout the entire sealed drug product shelf life to maintain CCI. However, excessive stopper compression may cause visual defects or crash CCS, which adversely affect the acceptance of a vial assembly.

Figure 4 shows example photos of rejectable visual defects caused by excessive stopper compression during the capping process that resulted in visual inspection failure on the manufacturing floor [8, 22]. Other defects caused by excessive stopper compression are possible. For example, excessive force can also crack glass vials and cause CCI failure.

In light of the multiple challenges associated with vial CCS performance, it is imperative to strike a balance when satisfying all CCS performance needs. CCS dimensional variations may lead

CCI must be stable under the multitude of potential circumstances that a vial product might encounter over its shelf life.

to capping failure, which results in CCS visual defects, CCI failure, or the potentially costly rejection of an entire CCS production batch. CCS stack-up optimization is designed to clearly define and locate a balanced window to satisfy both RSF and CCI while also providing an acceptable visual appearance. Figure 4 displays a balanced CCS performance window [8, 22], where the horizontal axis represents the stopper flange compression percentage and the vertical axis represents the seal skirt overhang length (defined by subtracting the summation of the stopper flange thickness and the vial flange thickness from the overall seal skirt length).

After completion of the capping process, the vial CCS stack-up dimension characteristics (in the rectangular shadowed area in the chart on Figure 4) of the vial assembly are described as follows:

- Seal skirt overhang length will depend on the original stopper flange thickness and its compression percentage, but it must be larger than the minimum overhang limit (horizontal red line in Figure 4) if the CCS components are to be properly assembled.
- To avoid the seal skirt wrinkling issue under the vial flange, seal skirt overhang length should be less than maximum overhang limit (horizontal dashed red line in Figure 4).
- Stopper flange compression percentage must surpass the lower compression limit to ensure sufficient RSF and to not exceed the MALL throughout the entire sealed drug shelf life for acceptable minimum CCI.
- Stopper flange compression percentage should not be excessive or beyond the upper compression limit to avoid visual defects such as, but not limited to, seal skirt wrinkling under the vial flange, stopper dimpling, seal side buckling, or a combination of these defects.

The stopper flange thickness, vial flange thickness, and seal skirt length are statistically variable data typically available from the CCS component manufacturers as a part of their routine quality assurance procedure. These CCS component dimension variables can be statistical input into calculations to evaluate the CCS's end performance and its quantitative failure risk in terms of its sealing performance and visual acceptance.

The statistical stack-up distribution curve can be calculated to not only identify the condition that suits a process but to also quantify the data-driven risk assessment of being outside the performance window (shadow area in Figure 4) over a range of conditions. As a result of the CCS stack-up, the seal skirt overhang length also becomes a statistical variable, in addition to its dependence on the actual stopper flange compression percentage. The statistical distribution of the overhang length is schematically represented as a blue curve in the Figure 4 chart, and it will move along the track between the blue line and the yellow line depending on the actual compression percentage. The goal is to ensure that the blue distribution curve of overhang length is positioned within the rectangular shadowed area on the chart in Figure 4, which is the optimal performance window. This will lead to the satisfactory CCS performance described earlier when correlated with CCI data. For data-driven risk management, the quantitative risk of being outside of the rectangular CCS performance window in Figure 4 can be calculated based on the actual statistical distribution of stopper, vial, and seal.

This mapping capability is powerful for pharmaceutical engineering applications because the cost of manufacturing defects can be high, ranging from the rejection of entire lots to product recalls. Using this real-data approach, the most probable assembly for each CCS can be identified, as well as the range of seal skirt overhang lengths encompassing any percentage of assemblies in the performance window at any stopper compression [8, 22]. In general, this comprehensive approach of stack-up calculations can assist in selecting and evaluating the compatible CCS components and appropriate stopper compression, as well as in troubleshooting CCS performance concerns and ensuring the process is operating within the optimal CCS performance window. This optimal performance window for CCS compatibility can be calculated, simulated, predicted, tested, and assessed for critical data-driven risk management, provided that sufficient CCS component data are available from the quality assurance database across CCS component manufacturers for life-cycle management.

CONCLUSION

A systematic pharmaceutical engineering approach for ensuring acceptable, compliant performance of vial CCSs must include choosing qualified CCS components, a proper capping process setup, and applicable testing methods. CCS performance includes both CCI and visual inspection acceptance. Characteristics of the elastomer stoppers play a critical role in delivering vial CCS performance through well-balanced material properties, overall CCS compatibility, and dimensional compressibility to accommodate the capping process window. The sealing performance of the elastomer stopper is inherently time- and temperature-dependent during the CCS shelf life, and cold temperatures may adversely impact CCI. Further considerations, which are beyond the scope of this article, include other environmental conditions (e.g., moisture, light exposure, handling, vibration, shock, impact). Using a systematic data-driven approach will aid informed decision-making when choosing compatible CCS components as well as ensuring they are assembled and tested in an appropriate manner to

minimize the potential risk for patient safety. Together, these steps will ultimately deliver a CCS that ensures a consistently high level of performance.

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