PHARMACEUTICAL ENGINEERING®

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64 *PHARMACEUTICAL ENGINEERING*® ARTICLE RECEIVES 2022 APEX AWARD

Pharmaceutical Engineering has won a 2022 APEX Award for Publication Excellence in the Technical & Technology Writing category for "AI's Promise for ATMPs," published in the November-December 2021 issue. The authors are William Whitford, Life Science Strategic Solutions Leader for DPS Group, and Toni Manzano, Co-Founder and CSO at Aizon.

This is the third year in a row that *Pharmaceutical Engineering*® has been recognized with an APEX Award.

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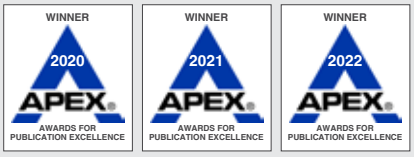

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By Jörg Zimmermann


Jörg Zimmermann

Heading Toward A New Annex 1 and ISPE Annual Meeting

Summer is over and we are all back to our workplaces. This year has been different than the two previous years with vaccination against SARS-CoV 2 decoupling the infection rates from hospitalization, intensive-care units, and fatalities. That is an unprecedented achievement in such short time, and we as the pharmaceutical industry have helped make it happen to get back to a new normal.

Travel for leisure and work has largely resumed, and at the same time, some form of mobile work has been carried over. This new flexibility helps balance work and life, but also requires a different self-discipline. How has it been for you? I have enjoyed traveling again very much, to the ISPE Europe Conference in Madrid and to universities in Germany and Austria for lectures. I was able to host the ISPE International Board of Directors at Vetter in Germany, and we visited friends and family in Italy and elsewhere. On the other hand, I was not able to spend as much time on my road bike as during the lockdowns—something has to give.

FOCUS ON REGULATORY AND QUALITY

This issue of *Pharmaceutical Engineering*® magazine has regulatory trends and quality initiatives as its theme. These two areas are core to ISPE's mission of bringing quality medicines to patients. ISPE is very active in commenting on draft regulations, both in the US and Europe, and the regulatory agencies listen to ISPE as an

Regulatory agencies listen to ISPE as an independent voice of the industry.

independent voice of the industry. Drug shortage prevention has been an area of work for the organization for about 10 years now, and it did not need the COVID-19 pandemic for our experts to be ready to show how more resilience can be built into the supply chains and to prevent shortages. With the current geopolitical situation, this continues to be of utmost importance.

ANNEX 1 REVISION

We should be holding a final version of Annex 1 in our hands now, which updates the regulations for sterile products manufacturing. This is one of the central documents

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What has transpired in the discussions is that both industry and regulators from different regions have positions that are defined by their culture and by their quality culture.

for our industry. As the latest version is issued concurrently by the European Medical Agency (EMA), World Health Organization (WHO), and Pharmaceutical Inspection Co-operation Scheme (PIC/S), it will set the standards worldwide. I have personally been involved in this and in the previous revision in 2006, where we as industry were able to convince the regulators to mandate grade A air supply for the crimping process for vials, instead of going to a straight grade A classification. This is just one example where the dialogue between industry and regulators has led to an acceptable path forward for everybody. The two rounds of consultations held for this revision were done with a large group of subject matter experts from ISPE involved in the commenting.

Jean-Francois Dulière, ISPE's European Regulatory Advisor, has been leading the group, consolidating hundreds of individual comments into an ISPE position. In panel discussions with regulators from around the world at conferences and webinars, the dialogue continued and helped enhance the understanding of some of the thinking and backgrounds. It remains to be seen if the high ambition to make a global document by EMA, WHO, and PIC/S will succeed or not.

What has transpired in the discussions is that both industry and regulators from different regions have positions that are defined by their culture and by their quality culture. There is not one industry position: yes, the products need to be sterile, but the requirements are different, whether producing small-volume parenterals and biologics or filling terminally sterilized infusion bags with saline and buffer solutions. Large Pharma, biopharma, start-ups, and manufacturers of advanced therapy medicinal products (ATMPs) need to adapt to the different requirements, while maintaining quality standards.

In my experience, while regulatory convergence and harmonization are a goal, agencies will focus on different aspects. In cultures where adherence to the word of the regulations is common, a manufacturer might say, "Tell me what to do. If you tell me 5, I will do 5. If you tell me 10, I will do 10. I do not need to understand it, but I am fulfilling the requirement, so I have to be in compliance. And on the other side of the spectrum are companies that have fully embraced International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q8, Q9, and Q10. They will therefore know exactly why maybe 6, 5 is the right value, and they will have scientific data to back it up and justify why using 6, 5 will lead to the right result.

Overall, there is great consensus on the principles of Annex 1, for example, on the contamination control strategy. While it has always been the goal of aseptic processing of sterile products to keep microbial, endotoxin, and particle contamination under control, the measures taken now also need to be described in an overarching strategy document. Putting this document together, starting with a process-and-gap analysis, makes companies rethink their processes and puts them in a better position to defend their systems.

ISPE ANNUAL MEETING

By now, your travel preparations for the 2022 ISPE Annual Meeting & Expo in Orlando, Florida, should be finalized. The committee has put together a fantastic program, covering regulatory and quality, digital transformation, manufacturing trends, supply chain optimization, therapy innovations, and many more topics.

I am very much looking forward to the keynote address by Thomas Wozniewski, PhD, Takeda's Global Manufacturing and Supply Officer. The story of a Japanese company becoming a truly global player with a number of acquisitions around the world is unique and learning about it firsthand will be most insightful.

Michael Kopcha, PhD, RPh, Director, Office of Pharmaceutical Quality, US Food and Drug Administration, will be talking about "Quality: A Key Ingredient for Stable Pharmaceutical Supply Chains" in the regulatory keynote address. In the general program, there will be sessions on everything from blockchain, aseptic processing, facilities, ATMPs to combination products. It will be difficult to choose which track to attend!

One thing I always enjoy at the Annual Meeting is the 5K, but this year, we are adding morning yoga and a golf tournament to the mix. The golf tournament will serve to collect donations to the ISPE Foundation, which means that some of the money will help students attend future events like the Annual Meeting in Las Vegas, Nevada, in 2023.

Orlando has a lot to offer besides the ISPE Annual Meeting, so why not take the opportunity to prolong your stay before or after the conference with a visit to Walt Disney World, SeaWorld Orlando, or Cape Canaveral?

I sure hope to see you in Orlando!

Jörg Zimmermann is Vice President, Vetter Development Service, External Affairs, at Vetter Pharma-Fertigung GmbH & Co., and the 2021–2022 Chair of the ISPE International Board of Directors. He has been an ISPE member since 2006.

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By Vivianne J. Arencibia


Vivianne J. Arencibia

THE RETURN OF IN-PERSON EVENTS BRINGS A PERSONAL TOUCH

Over the last two years, ISPE's Women in Pharma® (WIP) initiative remained undeterred in its mission to connect women throughout the global pharmaceutical industry. Through virtual engagement opportunities—including book clubs, Mentor Circles, webinars, and Sunrise to Sunset events—WIP has continued to create a forum for women to engage and inspire professional and personal development.

In recent months, life for many of us has taken a turn for the better. Slowly but surely, we've welcomed back a sense of normalcy and found ourselves with the deepest sense of appreciation, understanding what a privilege it is to be together once again. With this deep sense of gratitude guiding us, we've wasted no time in leveling up our WIP programming efforts.

NEW INITIATIVES

Under the leadership of Tanya Sharma, a WIP Steering Committee Member, we piloted the Think Tank concept at the 2022 ISPE Facility of the Future Conferences in February. This interactive, fully immersive concept is the latest WIP initiative and is meant to elevate and influence intellectual strength and leadership for pharmaceutical industry professionals of all backgrounds.

At the 2022 ISPE Biotechnology Conference, WIP sponsored an important panel discussion and workshop that successfully allowed for collaboration, synergy, and real-world problem-solving. A post on the iSpeak blog on 7 July provides a recap.

Delving further into real-world problem-solving, we doubled down on WIP's mission to bridge gender, cultural, and geographic barriers with our latest webinar, "Imperatives for Actionable Inclusion: Opportunities in the Workplace." Held on 14 June 2022, the webinar was moderated by WIP Steering Committee Chair Jennifer Lauria Clark and included a conversation with diversity, equity, and inclusion (DEI) experts Heather Rae Martin and Mishaune Sawyer. The webinar touched on DEI within the workplace as it applies to gender orientation, race, and unconscious biases.

We look forward to 2023 with high hopes and continued focus to elevate and empower women in the pharmaceutical industry worldwide.

ANNUAL MEETING

We continue to prepare for the 2022 ISPE Annual Meeting & Expo in Orlando, Florida, on 30 October–2 November. WIP will be hosting a professional development workshop entitled "Career Connections—Developing your Personal Brand" on 30 October.

This session will be led by Phil Gerbyshak, a LinkedIn Sales Trainer, sales expert, and talk show host of "The Sales and Leadership Show" on sales, leadership, and digital strategies and Kara Kirby, a leadership consultant, CEO of the Insights Leadership group, and podcast host of "Pop! On Leadership." The immersive, hands-on workshop will teach attendees how to evolve as a leader and develop their personal brand, including taking their personal LinkedIn profile to the next level. You'll discover how to create psychological safety allowing you to pursue your leadership potential, expand your confidence, and hone communication skills. We will explore the key components of psychological safety to establish authenticity, allowing for inclusivity to drive a more powerful work experience.

We'll also be hosting other networking events throughout the week including an evening event on 31 October and Morning Yoga on 1 November. These will be great opportunities to connect with new and old friends while recharging.

As we close out the year, we look forward to 2023 with high hopes and continued focus to elevate and empower women in the pharmaceutical industry worldwide. We encourage you to stay up to date with the latest WIP initiatives through our quarterly e-newsletter, *The Bridge*, where we provide important recaps and future engagements.

Vivianne J. Arencibia is Vice President, Global Quality Systems and Compliance, at Moderna, Co-chair of Women in Pharma®, and a member of the ISPE International Board of Directors and the ISPE Foundation Board. She has been an ISPE member since 1991.

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By Heather Bennett-Kelley


Heather Bennett-Kelley

BUILDING CONSENSUS

Most people in their careers have to work with others at some point, and in these work interactions there are exchanges of ideas. In pushing business processes forward, determining methodology for a new experiment, or designing a manufacturing facility, multiple stakeholders come from different points of view and with varying priorities. Working with others in any capacity and having the exact same approach and understanding to a problem as the other people is very rare. To make decisions, consensus needs to be gained.

The definition of consensus is the majority of opinion, general agreement [1], or group solidarity in sentiment and belief [2].

Why do we need to build consensus? As most of us do not live and work in a vacuum, we are not the only stakeholders in our lives. A stakeholder is one that has stake in an enterprise, or one who is involved in or affected by a course of action [3]. I am a project manager at a construction company. If my team is going to design and build a pharmaceutical manufacturing facility, there are many stakeholders, from the engineers designing the system to the facilities team that will be maintaining the piping once installed to the patient that may receive the life-saving medication that the plant manufactures. Not all of these stakeholders get a direct voice in design and construction decisions, but their voices do need to be considered. If someone feels their voice is not considered, then getting their buy-in is much more difficult and it might not stick even if they say yes.

CONVINCING OTHERS

How do you persuade people that your vision is worth agreeing with? You cannot make them, and if you do there likely will be resentment. Also, if you are a junior member on a team, you might not be able to make others follow your idea because you lack seniority.

An article from the *Harvard Business Review* [4] suggests some tips on how to get others to your side.

- Liking: Highlight similarities and offer sincere praise. If people like you, they are more apt to follow you. Also, if someone has an idea, recognize that idea within the team.
- Reciprocity: Give what you want to receive. First exhibit the behavior you wish to see. If you want others to be open to an idea, you need to listen and ask questions about the ideas of those you want to join you.
- Social proof: Use peer power when available. If someone on your team is already on board and the rest of the group is not convinced, that one team member could give their pitch about why they think it is a good idea.
- Consistency: Make commitments active, voluntary, and public. Once people make a written commitment, or their opinion is publicly announced, they are more likely to stick with that opinion.
- Authority: Don't assume your expertise is known. If you have a certificate in an area that shows knowledge of the subject about which you are trying to convince others, post this in your office or reference the certificate in your introduction slide of a presentation.
- Scarcity: Exclusivity of opportunity or information goes a long way. People want in on what is rare.

These approaches are best used in conjunction with each other, according to the article. These could also open the door for opportunities that might not otherwise be available.

Good luck with your consensus-building!

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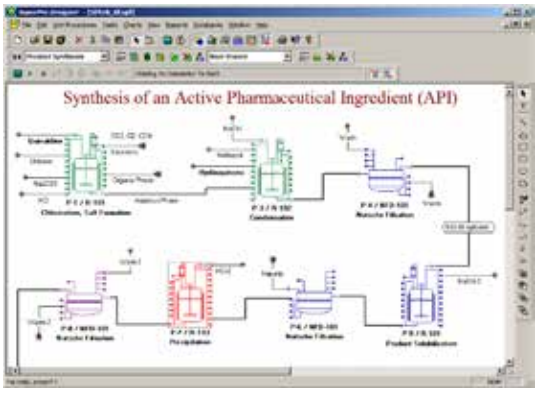

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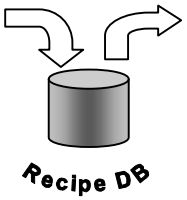

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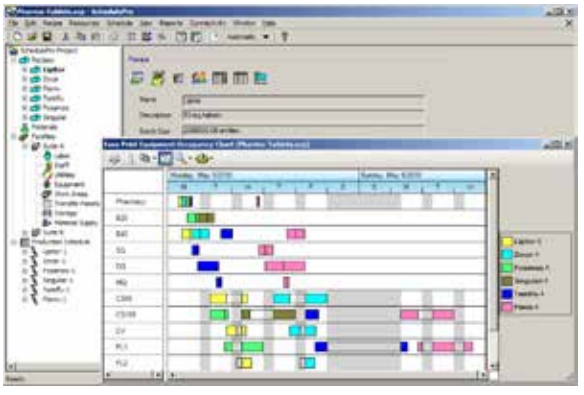

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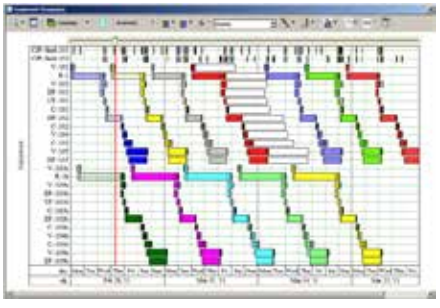

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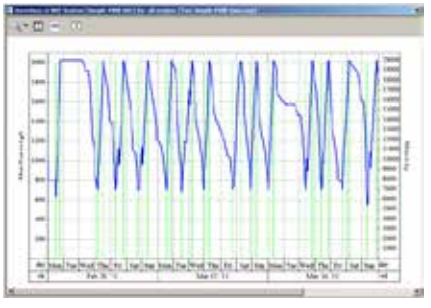

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SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor,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

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IS A GLOBALLY HARMONIZED QUALITY OVERALL SUMMARY POSSIBLE?

By Beth Kendsersky, Jennifer L. Brown, Connie Langer, and Roger Nosal

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline on Registration of Pharmaceuticals for Human Use (M4) [1] offers advantages in the consistent format of the registration dossier using the Common Technical Document (CTD). However, it does not deliver a comprehensive view of the overall manufacturing control strategy or a means of understanding and managing the quality of the product throughout its life cycle. As a result, several regulatory authorities that have implemented the CTD format have also insisted on supplementary quality summary documentation that exceeds ICH requirements, and, in effect, creates divergent expectations for chemistry, manufacturing, and controls (CMC) content. A single global quality overall summary (QOS) format could clearly convey a holistic view of a product's control strategy and improve the efficiency and economy of the regulatory review of an application while providing a way for the applicant and reviewer to align on a product life-cycle management plan.

The current structure and format of the QOS does not provide a mechanism to holistically integrate the elements of the control strategy in the CTD. This, and the need for review efficiency, has prompted several regulatory authorities to implement their own unique summary document formats and requirements to facilitate their reviews. These redundant summary documents diverge in scope and demand varied information be included in the registration application for different countries, which can result in a delays in submission, approval, and availability of critical medicines to patients worldwide.

This article endeavors to capture the rationale and purpose for the multitude of CMC summary documents required in various countries and offers a proposal for how a more holistic and comprehensive QOS could be structured while leveraging the concepts and tools outlined in ICH Q12, specifically the sections on "Established Conditions" (ECs) and the "Product Lifecycle Management" (PLCM) document.

A consistent content and format for the QOS could lead to harmonized marketing authorization (MA) filings globally and streamlined regulatory authority assessments of quality information. The proposal for a more holistic and comprehensive QOS will provide a mechanism for industry to convey a holistic view of their ECs and control strategies and could increase consistency and efficiency in regulatory decision-making and actions, which would facilitate timely approvals and accelerate access of new drugs to patients.

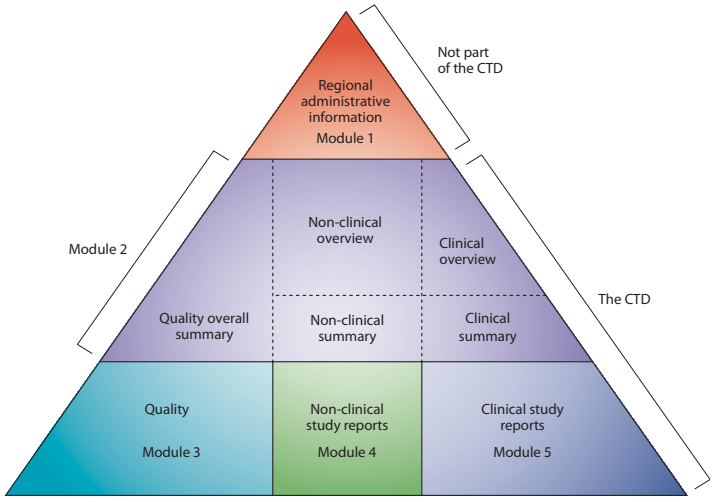
REGULATORY LANDSCAPE

ICH has now grown to include 17 members, and guidelines are being adopted by a growing number of regulatory authorities [2].

The ICH website provides a summary of the self-declaration of the regulator regarding the conclusion of the implementation process. A status of "implemented" implies the process of implementation is completed. The following agencies [3] have declared implementation of the ICH Guideline: The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality ICH M4Q (R1) [1] and M4Q Q&As (R1)—Questions & Answers CTD on Quality [4]:

- Brazil National Health Surveillance Agency (ANVISA), Brazil
- EC, Europe

Figure 1: The CTD triangle (© ICH) [6].



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.

- Food and Drug Administration (FDA), United States
- Health Canada, Canada
- Health Sciences Authority (HSA), Singapore
- Ministry of Food and Drug Safety (MFDS), Republic of Korea
- Ministry of Health, Labour and Welfare/Pharmaceutical and Medical Device Agency (MHLW/PMDA), Japan
- National Medical Products Administration (NMPA), China
- Swissmedic, Switzerland
- Taiwan's Food and Drug Administration (TFDA), Chinese Taipei

The Quality sections of the CTD include detailed CMC information in Module 3 (M3) and a summary of the CMC information in Module 2 (M2, or QOS).

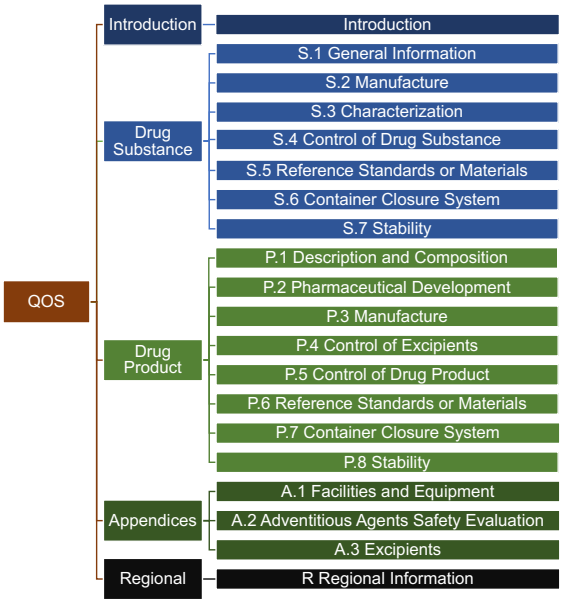
While the current CTD structure offers some advantages in the harmonized format of registration dossiers, challenges with the format and content of the QOS exist in several countries as reflected by the requirement for specific templates and/or additional content not required by ICH M4Q.

CHALLENGES WITH THE QOS STRUCTURE

The ICH M4 (R4) guideline, Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use [5], describes the CTD as five modules. As shown in Figure 1, the CTD is the format implemented in multiple ICH regions. ICH M4Q (R1) provides guidance on how to structure both M3 and the QOS, which links to more detailed quality data and information in M3.

Options for granularity are provided in the ICH M4 (R4) guideline for the QOS. These options range from a single QOS containing a summary of all quality information to a QOS that is systematically organized in alignment with the granularity of M3. There is one M2 section corresponding to each major M3 section and appearing in the same sequential order, as illustrated in Figure 2.

Figure 2: Granularity options for the QOS described in ICH M4Q (R1).



Regardless of how the quality information is summarized, there should be no CMC content included in the QOS that is not also included in the M3 Quality CTD sections. It is important to note that the QOS content is generally not maintained after the initial marketing authorization approval or throughout the life cycle of the product. The QOS document(s) that accompany the CTD application is/are typically copied and pasted from the data in the corresponding M3 sections and may be used by some regulators as the basis for their initial review template. From an industry perspective, the QOS has not been considered very useful to present a holistic view of a product's control strategy.

ONGOING QOS-RELATED INITIATIVES

Several ongoing initiatives should be considered in the development of a harmonized QOS.

US FDA White Paper

In 2018, the FDA authored a white paper indicating the agency's desire to use the QOS as a tool to "improve the efficiency and quality of the regulatory assessment" and to "communicate essential aspects of the application" [7]. As the typical QOS is copied and pasted from M3 sections, it presents a very segmented and incomplete view of a product's control strategy. Ideally, the alignment of the QOS content across the ICH regions would focus the application assessment on the importance of the drug substance and drug product control strategies and summarizing the regulatory commitments.

ICH M4Q Revision

In 2020, the ICH Assembly supported a proposal to revise ICH M4Q: The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality–M4Q (R1), Quality Overall Summary of M2, M3: Quality [8]. The M4Q (R2) Informal Working recently approved its Concept Paper and Business Plan [9, 10]. Specifically, the working group will reorganize the CTD Quality sections in M2 and M3 to capture submitted information on drug substance and drug product specifications, characterization and control of impurities, analytical testing and validation, stability data, manufacturing process and unit operations, associated manufacturing facilities, and container closure system in an organized structure consistent with modern pharmaceutical manufacturing and regulatory guidance.

Structured Product Quality Submissions (SPQS)

Algori, et al., suggested structured content management (SCM) as an opportunity for enhancing review and organization of documents by providing the framework for authoring content that is easy to adapt into multiple documents and standardize [11]. Using XML-based systems for the management of CMC data provided in the CTD in M2 and M3 quality sections have also been proposed by some regulators to facilitate a more highly structured assessment as compared to today's narrative approach to submission and review. In June 2018, the FDA announced a knowledge-aided assessment and structured application (KASA) initiative as a new review platform to modernize generic drug review from a text-based to a data-based assessment and to promote robust generic entry [12].

Leveraging structured content management could potentially streamline the summary of quality data in regulatory submissions and was also supported as a new topic proposal at the ICH Assembly virtual meeting in 2020 [8]. Structured data using XML-based systems have been used to enhance regulatory review and to harmonize the organization of registered content. This allows for information classification and re-use of content that contains descriptive metadata to aid in structuring and presentation of data elements. A structured platform could also enable automated analysis of some portions of the application, which would save time and ensure consistency.

A successful implementation of any structured product quality submission for CMC content will require significant global collaboration and alignment, as well as coordination with other ongoing proposals to revise CTD M2 and M3. When proposing to harmonize the global regulatory requirements for CMC summary documents, the ongoing efforts to implement SPQS and revise the ICH M4Q M2 and M3 content guideline(s) must both be considered. Ideally, the use of XML for the management of CMC data provided in M3 could facilitate the generation of any format for a summary document required by a regulator as a review template.

ISPE Regulatory Quality Harmonization Committee (RQHC)

The mission of the ISPE RQHC North America group is to anticipate, engage with, and facilitate technical implementation of regulatory guidance and expectations in North America to the benefit of ISPE members and stakeholders [13]. A subcommittee of this group is developing proposals on the content and structure of a risk-based QOS that could ultimately standardize CMC terminologies and submission standards for control strategy harmonization and cloud assessment.

Implementation of ICH Q12

The ICH Q12 guideline, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, is in the process of implementation for ICH members [14]. Once implemented, the framework described in Q12 "to facilitate the management of post-approval CMC changes in a more predictable and efficient manner"[14] and the tools and approaches (including ECs and the PLCM document) can play an important role in the development of a comprehensive QOS. ECs, which are defined as "legally binding information considered necessary to assure product quality" allow a clear understanding between the marketing authorization holder and the regulatory authorities on which elements of the control strategy assure product quality, and which information can be designated as supportive [14].

The PLCM document summarizes the ECs, and once approved, serves as an agreement between the market authorization holder and the regulatory authority on the reporting category for future changes to those ECs. In instances where ECs are being proposed across the whole of M3, the PLCM document, along with a narrative that justifies the overall control strategy, could be used to form the basis of a comprehensive QOS that provides an accurate record of key data necessary to assure product quality and documents the reporting categories necessary to change it. The option to include the ECs within the context of the PLCM document in a single global format could also eliminate the need for unique regional CMC summary documents.

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EVALUATION OF REGIONAL CMC SUMMARY DOCUMENT

Several unique summary documents are required per some regulatory authority regulations that (a) may not follow the standard ICH QOS CTD format; (b) are above and beyond the QOS CTD requirements; (c) represent commitments or ECs; and (d) must be maintained throughout a product's life cycle. Some of the more commonly known types of compliance summary documents include the Canadian Certified Product Information Document (CPID), the Japan Application Form (AF), and the Russian Normative Document (ND). Depending on the country, the level of M2/3 content required in the respective summary documents may differ.

CMC Requirements in Bespoke Compliance Summary Documents

CMC requirements for compliance summary documents were compared for this article for several countries, noting that some regions leveraged the same templates/requirements across several countries. For each country in scope of this evaluation, the following questions were addressed: (a) why do the regulators require CMC summary information in their specific format?; (b) is the submission of CMC information in this format considered mandatory?; (c) is the summary document considered a compliance document/must it be maintained after approval?; (d) what quality information is required in the compliance summary document?; and (e) is the quality information required in the compliance summary document beyond the ICH M4Q M3 information required?

A summary of the results from this evaluation is provided in Table 1 and Table 2. The summary in Table 1 is based on an interpretation of the respective country guidance documents for the summary documents, where available. A summary of the CTD M3 sections that would contain the technical content required in each of the regional compliance summary documents is provided in Table 2. In contrast to the segmented ICH M4Q(R1) QOS in Figure 2, the proposed QOS would provide the holistic view of the entire dossier and would highlight risks and provide links to more detailed information in M3. It would bring together all of the elements of the development experience and culminate in a comprehensive picture of the overall control strategy and cohesive narrative on how the ECs were determined and justified.

The majority of the CMC compliance summary documents require information from CTD sections that contain information as described in Appendix 1, Table A of ICH Q12 [14], e.g., nomenclature, structure, manufacturer, manufacturing process, which is reflected in the "Proposed" column in Table 2. Here is a brief summary of the purpose and required information (including information not described in ICH Q12 Appendix 1, Table A) for each CMC compliance summary document.

- The Canadian CPID is a condensed summary of the key quality (drug substance and drug product) information provided in NDS applications. In addition to the compliance information, the CPID also includes drug substance general properties, impurities, process validation, and stability information, but it does not include drug substance nomenclature, control of materials, control of critical steps and intermediates, analytical procedures, reference standards, or drug product excipient information, analytical procedures, or reference standards content.

Table 1: Rationale for CMC compliance summary documents required by various health authorities (as of June 2021).

Country/Health Authority	Name of CMC Compliance Summary Document	Rationale for Unique Summary Document Format	Mandatory?	Must Be Maintained After Approval?
Canada/Health Canada	CPID: Certified Product Information Document – Chemical Entities (CPID-CE) [15]	• To provide a condensed summary of the QOS and to represent the final, agreed-upon key data from the new drug submission (NDS) review [e.g., identification of the manufacturer(s), drug substance/drug product manufacturing process and controls and specifications, stability conclusions, commitments] • To provide an accurate record of key quality information for the product proposed for marketing at the time the notice of compliance (NOC) is issued, and thereafter serves as an official reference document during the course of post-approval inspections and postapproval change evaluations • Structured to permit the rapid assembly of the CPID-CE by copying requisite information from the corresponding portions of the QOS filed with the original NDS	Yes	Yes
China/NMPA	Drug Product Manufacturing Process Information Sheet (MPIS)/ Annex 2[7] [16]	• The MPIS serves as the basis of GMP site inspections	Yes	Yes

table continues next page

Table 1 continued

Country/Health Authority	Name of CMC Compliance Summary Document	Rationale for Unique Summary Document Format	Mandatory?	Must Be Maintained After Approval?
Japan/PMDA	Application Form, AF [17]	• To distinguish and establish in advance the matters to be addressed in a partial change approval application or a minor change notification for the approved matters at the time when the manufacturing method is changed • Notification or application for a postapproval change is required for any changes made to the approved content in the AF	Yes	Yes
Republic of Korea/MFDS, formerly known as the Korea Food and Drug Administration (KFDA)	CMC Summary Document[8] [18]	• Undetermined	Yes	Yes
South Africa/South African Health Products Regulatory Authority (SAHPRA)	Summary of Critical Regulatory Elements (SCoRE) [19]	• To facilitate review of new applications and to reduce evaluation time	Yes	Yes
Eurasian Economic Union (EAEU)1 /Ukraine Uzbekistan	Quality Normative Document [20]	• To facilitate local testing • To provide an accurate record of key quality information for the product proposed for marketing, and thereafter to serve as an official reference document during the course of postapproval inspections and postapproval change evaluations • When medicines are imported into the Russian Federation, certification from the manufacturer stating that the imported medicine is in compliance with the pharmacopeia monograph or with the normative document is required	Yes	Yes
Ethiopia, Gulf Cooperation Council (GCC)[2], Ghana, Nigeria, Pakistan, Rwanda, SADC[3]/Various	World Health Organization (WHO) QOS[5] [21]	The QIS and QOS: • Constitute a mandatory part of the registration application dossier, life cycle, and renewal applications • Provide an accurate record of technical data in the product dossier at the time of registration • Serve as official reference documents during the course of GMP inspections, variation assessments, and renewals	Yes but some markets may accept ICH M4Q M2 format	Varies[6]
Ghana, Nigeria, and South African Development Community (SADC)[3] /Various	WHO quality information summary (QIS)[5] [22]			
ICH Countries/Various	ICH M4Q Module 2 ICH M4Q (R1) [1] Core ICH Q12 Guideline ECs, PLCM,[4] and annexes [14]	• ECs and the PLCM are not required by the Board of Health: If a marketing authorization holder (MAH) decides to use this tool to demonstrate how increased product and process knowledge can contribute to a more precise and accurate understanding of which postapproval changes require a regulatory submission as well as the definition of the level of reporting categories for such changes, they can use this document to communicate these proposals	No	Yes, if filed

[1] EAEU includes the following markets: Armenia, Belarus, Kazakhstan, Kyrgyzstan, and Russia.

[2] GCC includes the following markets: : Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates.

[3] SADC includes the following markets: Angola, Botswana, Democratic Republic of Congo, Eswatini, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Tanzania, Zambia, and Zimbabwe.

[4] Implementation of ICH Q12 is in progress among ICH members and observers.

[5] Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part and quality information summary (QIS) guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part.

[6] Several markets have developed unique national guidance and templates based on the WHO guidance to require the submission of a WHO QOS and/or QIS template in the initial marketing application. However, these countries may vary with respect to whether they consider these documents as commitments that must be maintained/updated with each subsequent variation.

[7] There is no official English version of the MPIS template available on the CDE/NMPA website.

[8] No specific regulation or guidance exists on the requirements for Republic of Korea CMC Summary; however, based on authors' experience and regulatory queries we have included in our evaluation. The reference is to a parent guidance.

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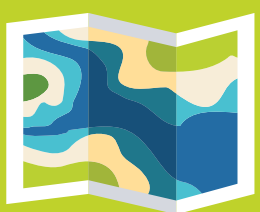

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Table 2: Regional CMC compliance summary requirements aligned with CTD quality sections.

SUMMARY DOCUMENT REQUIREMENT CTD SECTION	WHO	CANADA	CHINA	JAPAN	REPUBLIC OF KOREA	SOUTH AFRICA	EAEU	PROPOSED[1]
S11 NOMENCLATURE	Y	N	N	Y	Y	Y	Y	Y
S12 STRUCTURE	Y	Y	N	Y	Y	Y	Y	Y
S13 GENERAL PROPERTIES	Y	Y	N	N	N	Y	N	N
S21 MANUFACTURER	Y	Y	N	Y	N	Y	N	Y
S22 MANUFACTURING PROCESS	Y	Y	N	Y	N	Y	N	Y
S23 CONTROL OF MATERIALS	Y	N	N	Y	N	Y	N	Y
S24 CONTROL OF CRITICAL STEPS & INTERMEDIATES	Y	N	N	Y	N	N	N	Y
S25 PROCESS VALIDATION & EVALUATION	Y	N	N	N	N	N	N	N
S26 MANUFACTURING PROCESS DEVELOPMENT	Y	N	N	N	N	N	N	N
S31 ELUCIDATION OF STRUCTURE	Y	N	N	N	N	Y	N	N
S32 IMPURITIES	Y	Y	N	N	N	Y	N	N
S41 SPECIFICATION	Y	Y	Y	Y	Y	Y	N	Y
S42 ANALYTICAL PROCEDURES	Y	N	Y	Y	Y	N	N	Y
S43 VALIDATION OF ANALYTICAL PROCEDURES	Y	N	N	N	N	Y	N	Y[2]
S44 BATCH ANALYSES	Y	N	N	N	N	Y	N	N
S45 JUSTIFICATION OF SPECIFICATION	Y	N	N	N	N	N	N	N
S5 REFERENCE STANDARDS OR MATERIALS	Y	N	N	Y	N	Y	N	Y
S6 CONTAINER CLOSURE SYSTEM	Y	Y	N	Y	N	Y	N	Y
S71 STABILITY	Y	Y	N	Y	N	Y	N	Y
S72 POST APPROVAL STABILITY PROTOCOL & COMMITMENT	Y	N	N	Y	N	N	N	N[3]
S73 STABILITY DATA	Y	N	N	N	N	N	N	N
P1 DESCRIPTION AND COMPOSITION	Y	Y	Y	Y	Y	Y	Y	Y
P2 PHARMACEUTICAL DEVELOPMENT	Y	N	N	N	N	Y	N	N
P31 MANUFACTURERS	Y	Y	N	Y	N	Y	Y	Y
P32 BATCH FORMULA	Y	Y	N	Y	N	Y	N	Y
P33 MANUFACTURING PROCESS & CONTROLS	Y	Y	Y	Y	Y	Y	N	Y
P34 CONTROL OF CRITICAL STEPS & INTERMEDIATES	Y	Y	Y	Y	N	Y	N	Y
P35 PROCESS VALIDATION	Y	Y	N	N	N	Y	N	N
P41 EXCIPIENT SPECIFICATION	Y	N	Y	Y	Y	N	N	Y
P42 EXCIPIENT ANALYTICAL PROCEDURES	Y	N	Y	Y	Y	N	N	Y
P43 EXCIPIENT VALIDATION OF ANALYTICAL PROCEDURES	Y	N	Y	N	N	N	N	Y[2]
P44 EXCIPIENT JUSTIFICATION OF SPECIFICATION	Y	N	N	N	N	N	N	N
P45 EXCIPIENTS OF HUMAN OR ANIMAL ORIGIN	Y	N	N	Y	N	N	N	Y
P46 NOVEL EXCIPIENTS	Y	N	N	N	N	N	N	Y
P51 SPECIFICATION	Y	Y	Y	Y	Y	Y	Y	Y
P52 ANALYTICAL PROCEDURES	Y	N	Y	Y	N	N	Y	Y
P53 VALIDATION OF ANALYTICAL PROCEDURES	Y	N	N	N	N	Y	N	Y[2]
P54 BATCH ANALYSES	Y	N	N	N	N	Y	N	N
P55 CHARACTERIZATION OF IMPURITIES	Y	N	N	N	N	N	N	N
P56 JUSTIFICATION OF SPECIFICATION	Y	N	N	N	N	N	N	N
P6 REFERENCE STANDARDS OR MATERIALS	Y	N	N	Y	N	Y	N	Y
P7 CONTAINER CLOSURE SYSTEM	Y	Y	Y	Y	Y	Y	Y	Y
P81 STABILITY SUMMARY AND CONCLUSIONS	Y	Y	N	Y	Y	Y	Y	Y
P82 POST APPROVAL STABILITY PROTOCOL & COMMITMENT	Y	Y	N	Y	N	Y	N	N[3]
P83 STABILITY DATA	Y	Y	N	N	N	Y	N	N

[1] Proposal for a global summary document based on the ICH Q12 guideline on ECs.

[2] If performance-based ECs for analytical procedures are included in the application, then elements of the validation would need to be included as an EC.

[3] CMC regulatory commitments (e.g., stability, postapproval CMC commitment) made by a marketing authorization holder (MAH) to provide data or information to the regulatory agency in a market authorization application is considered supportive information.

- The China MPIS is drafted by the applicant, reviewed with the initial marketing application, and then issued by the NMPA with product approval. It includes key compliance information on the drug substance (specifications and methods) and drug product (formulation, manufacturing process, specifications, methods, and container/closure).
- Although no specific regulation or guidance could be found on the requirements for the Republic of Korea CMC Summary, the authors' experience through the receipt of regulatory queries has indicated this document is required. The Republic of Korea's summary document primarily contains drug substance general information and specifications, drug product composition, excipient information, manufacturing process, container closure, and stability conclusions. The Republic of Korea also has a unique requirement to include the storage condition for non-compendial excipients in their compliance summary document.
- The South Africa SCoRE document is a relatively new requirement from the South Africa Health Products Regulatory Authority and is intended to facilitate review of new applications and to reduce evaluation time. In addition to the compliance information, the South Africa SCoRE document also includes drug substance general properties, elucidation of structure, impurities, and batch analysis content and drug product pharmaceutical development, process validation, batch analysis, and stability content but does not include drug substance, control of critical steps and analytical procedures or drug product excipient, or analytical procedures content.
- The Japan Application Form (AF) is a summary of many of the M3 sections, especially those focused on manufacturing commitments. Importantly, the Japan AF includes information for each manufacturing parameter to facilitate future postapproval changes; for each parameter's target or set value, the use of 『』 or 《》 around each value indicates whether a future change to this parameter would be a minor change notification or partial change application, respectively. In addition to the AF, the PMDA also requires specific tables (Module 1.13, Table 1 and Table 2), which describe and justify the designation of manufacturing process parameters and acceptable ranges, which also facilitate postapproval changes. The CMC content in the Japan AF is the most closely aligned with the compliance information listed in ICH Q12 and with the content of the proposed QOS.
- The EAEU Quality Normative Document (QND) is different from the summary documents being discussed and includes not only a list of quality characteristics of the product but also quality control methods for a medicine, intended to facilitate local testing. Given the QND's specific purpose, the proposed QOS may not readily replace this particular compliance summary document.
- The WHO QOS product dossier template is required by multiple Africa/Middle East (AfME) markets, as well as by Pakistan. The WHO QOS is a comprehensive document, with content the same as the required by ICH M4Q(R2), but in a different format and in a different template. Therefore, the WHO QOS could easily be replaced by the proposed QOS.

In general, the compliance summary documents summarized in Tables 1 and 2 are required *in addition to* what is required in ICH M4Q (R1) as part of the initial marketing application. These compliance summary documents are primarily intended by the various regulatory authorities to facilitate their review of the initial marketing application, and also, importantly, to facilitate the review of subsequent postapproval changes by documenting key quality information (e.g., commitments or ECs) in a standardized and summarized format. As noted in Table 2, except for the WHO QOS document which contains CMC content exactly in accordance with ICH M4Q (R1), the CMC content in the remaining compliance summary documents are a subset of the content required by ICH M4Q (R1).

CMC Documentation Requirements Beyond Content in M3

In addition to summaries of the "standard" quality content noted in Table 2, many of these compliance summary documents also require additional information above and beyond the ICH M3 requirements. This "extra" information may require life-cycle management. Table 3 summarizes these additional requirements for the markets within the scope of this article.

For example, the EAEU QND requires details of the drug product analytical methods to facilitate local testing. The Canada CPID, the South Africa SCoRE, and the WHO QOS require the drug product master batch record numbers, which are available at the manufacturing site upon inspection. These three compliance summary documents also include entries for the drug product process validation (PV) report and protocol document numbers, but this requirement could be addressed by providing the PV protocols and/or reports for review upon request.

The China MPIS has several unique requirements beyond the standard ICH M3 content, including that the excipient and packaging manufacturers and the China Drug Master file (DMF) numbers be listed, as well as a list of drug product manufacturing equipment. Notably, also required is the compendia version to which each compendial excipient complies, when it is broadly understood that each compendial excipient will comply with the compendia current at the time of the excipient's use, without the need to update the drug product application. In addition to the MPIS, China also requires a specification/method document known as the "JX" for small molecules, which can also be considered a summary compliance document since it is a summary of M3 information that is required to be maintained after approval, but this document has been omitted for the purposes of this paper as its intent is for import testing.

DISCUSSION

Regulators need a comprehensive, coherent description of the product control strategy [7] and an understanding of life-cycle change management, while industry needs to manage inconsistency in regulatory assessments and regulatory commitments for the same global product.

Table 3: Regional compliance summary document requirements beyond CTD M2/3 (requiring life-cycle management).

Document Requirement	Canada	China	Japan	Republic of Korea	South Africa	EAEU	WHO[1]	Proposed
Detailed drug product (DP) analytical methods						X		
Packaging process information					X			
DP master batch record numbers	X				X		X	
Storage conditions for non-compendial excipients				X				
Excipient manufacturers		X						
Excipient registration numbers (China DMF)		X						
Packaging component manufacturers		X						
Packaging registration numbers (China DMF)		X						
DP equipment details		X			X			
Excipient compendial reference (including version)		X						
DP in-use period								
Name/address of corporate headquarters			X					
Name, position, education, and signature of person in charge at all sites listed in 3.2.P.3.1, as well as statement of commitment								
Quality certificate for each site listed in 3.2.P.3.1			X					
Japan Module 1.13 Tables 1 and 2 with details of parameters and acceptable ranges			X					
PV protocol or report number	X				X		X	
Specific drug substance aqueous solubility					X		X	
Drug substance specification number at DP manufacture site	X				X		X	
DP specification number at DP manufacture site	X				X		X	

[1]Requirements for content of WHO QOS may vary per market.

Challenge

While the QOS has been effective in certain ways, its ineffectiveness has led to requirements to provide additional summary documents (e.g., Canada CPID, China MPIS, Japan AF, Republic of Korea Summary document, South Africa SCoRE, and EAEU QND) beyond the QOS. These countries currently require a market authorization holder to provide specific summary documents as part of the regulatory submission and approval process for a new drug application.

In some cases, these summary documents contain the same information that is provided in the QOS sections in M2 and are therefore additional administrative tasks, which can create delays in submission and subsequent approval. In other cases, these documents require CMC information beyond what is required in the QOS and M3. For all of the countries discussed here, these additional summary documents represent commitments and must be maintained throughout a product's life cycle, above and beyond the M3 documents. The provision and maintenance of additional market-specific summary documents is not conducive to supporting a harmonized QOS and presents an additional burden on industry.

Proposed Solution

Given that the purpose of these market-specific summary documents (with the exception of the EAEU QND) is to facilitate review of both the initial marketing application and subsequent post-approval changes, a single summary document could replace the QOS as well as each of these individual summaries.

Such a summary document has the potential to be an even more effective tool to significantly improve the efficiency and quality of the regulatory assessment. To do this, it needs to (a) efficiently describe the product development process in the context of mitigation of risk to the patient; (b) provide a clear summary of the overall control strategy as part of the risk mitigation or control; (c) guide the regulator through the fragmented content to the submission [7]; and (d) elucidate the life cycle management plan for the product.

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An opportunity exists to propose a summary document that does the following:

- Frames the drug development story by effectively conveying how enhanced process understanding, product knowledge, and risk assessments are linked to a comprehensive control strategy
- Links the drug substance and drug product critical quality attributes (CQAs) to target product profile (TPP) and quality target product profile (QTPP)
- Summarizes the holistic control strategy, including links to more detail in M3, demonstrating how the proposed manufacturing process and controls (namely, critical process parameters, critical material attributes, and ECs) will provide assurance a drug substance and drug product will meet their respective CQAs
- Declares and documents a summary of the ECs and a proposed PLCM, if applicable, can also be leveraged

A globally harmonized summary document that defines regulatory commitments, justified within a more comprehensive QOS document fulfilling global regulatory requirements, would benefit the regulators, industry, and most importantly, the patients. A comprehensive QOS that summarizes the product development in a narrative that connects the material attributes, process, and product understanding to the overall control strategy could improve the efficiency and economy of regulatory review and assessment of an application globally. In addition, the option leverages tools in the ICH Q12 guideline on "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" [14] in a single format that could provide regulators with a concise, risk-based submission summary highlighting a product's control and lifecycle strategy, decreasing review and approval timelines, and enabling faster availability and sustained supply of critical medicines to patients worldwide.

CONCLUSION

The provision of market-specific compliance summary documents as part of the regulatory submission and approval process for a new drug application is considered beyond ICH requirements. In addition, effectively conveying enhanced process understanding and product knowledge in a regulatory application has been a challenge for both regulators and industry. A globally harmonized QOS in a regulatory submission that contains a comprehensive summary of the product development and control strategy, clearly listing all CMC commitments and how changes to them will be managed throughout the life cycle of a product, can address both of these challenges and would benefit regulators, industry, and patients by:

- Providing a relevant and risk-based summary of the entire CMC section of the marketing application and accelerating the regulatory action and decision-making process
- Facilitating approval of drug applications and improving the speed of patients' access to new drugs
- Providing a succinct summary of the data to justify and confirm that the ECs are adequate to ensure product quality, building confidence in a product's overall control strategy
- Clearly identifying the CMC regulatory commitments and eliminating the need for country-specific summary documents
- Leveraging the concepts and tools outlined in ICH Q12 to facilitate/simplify the management of post-approval CMC changes and enable continuous improvement and supply

The ICH Assembly finalized and released training modules on the ICH Q12 Guideline on Regulatory and Technical Considerations for Pharmaceutical Product Lifecycle Management on 10 June 2021. In addition, the 2020 ICH Assembly supported work on new topic proposals of CTD and Structured Product Quality Submissions, which is underway [8].

Therefore, the timing is perfect to address the current challenges with the implementation of ICH M4Q (M2) expressed in this paper and to develop a globally harmonized QOS that benefits regulators, industry, and patients and eliminates the provision and maintenance of additional market-specific summary documents.

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Streamlining Postapproval Submissions USING ICH Q12 AND SCDM

By Jackie Gavin, PharmD, Jessica Lo Surdo, PhD, Nina S. Cauchon, PhD, Tabetha M. Bonacci, PhD, and Michael J. Abernathy

Postapproval change management of pharmaceuticals is an essential part of life-cycle management but is associated with regulatory challenges. Incorporating concepts and tools from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q12 guideline, combined with structured content and data management (SCDM) and a cloud-based data exchange platform, could provide synergistic benefits that will enable efficient supply maintenance of life-saving therapies worldwide.

Following approval of an initial marketing application, postapproval changes are needed to ensure adequate supply, mitigate supply risk, expand patient market access, optimize manufacturing processes, improve analytical methods, and comply with new regulatory expectations. Regulatory submission and evaluation of chemistry, manufacturing, and controls (CMC) data may be required for changes that have a higher risk to impact product quality. Such changes can include increasing batch sizes, adding manufacturing facilities, creating new product presentations, and updating analytical methods. Prior to implementation of a change, manufacturers conduct risk assessments and generate data to confirm there would be no adverse impact to product quality through shelf-life as a result of the change [1, 2].

Health authorities have specific regulations and guidelines that govern reporting requirements necessary to implement postapproval variations; however, regulatory submissions for a given change can vary based on differing regional requirements as specified by the health authority conducting the review. For changes requiring approval before implementation, once the necessary information has been submitted across regions, each health authority must review the data package and documentation based on local requirements.

The timing and data requirements vary depending on the reporting category, submission, and legal obligations in each individual jurisdiction. For products with a large global footprint, the time required from submission to global approval and implementation of a single change can take years while the change obtains approval across all the relevant regulatory agencies. The resulting complexity requires manufacturers to tightly control and manage supply chain activities for commercial products globally to maintain compliance [1, 2]. Depending on the nature of the change, manufacturers may be required to maintain both the pre- and post-change equipment, processes, or methods until all approvals are received.

In an attempt to address these challenges, in 2019 the ICH endorsed ICH Q12, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (and Annexes). This guideline was developed and designed to provide a flexible framework to facilitate postapproval CMC change management, and outlines a risk-based, structured, and harmonized approach [3, 4].

The current lack of global harmonization for CMC content across regions requires the burdensome task of creating multiple submissions to fulfill varying regulatory requirements across different markets. Typically, CMC information needed to support a postapproval submission is accessed and transcribed manually from raw data systems (e.g., laboratory notebooks, batch records, and technical reports) to submission documents (e.g., Common Technical Document [CTD] sections). This information package is then submitted in electronic PDF format that health authorities

must manually "unpack" or deconstruct in order to perform their assessments. These efforts consume substantial time and resources for both sponsors and health authorities, which may result in redundancies and the need for multiple data integrity checks. The use of SCDM can potentially help alleviate the burden of submission authoring by shifting the focus from document management to data management, including how information is stored, analyzed, authored, and reviewed [2, 5].

This article will examine the current global regulatory submission workflow for postapproval CMC changes and will propose principles to streamline regulatory submission authoring through the utilization of ICH Q12 concepts, in combination with SCDM. It will also discuss several challenges associated with full implementation of the ICH Q12 regulatory tools, including established conditions (ECs), postapproval change management protocols (PACMPs), and product life-cycle management (PLCM) documents. Other challenges addressed in this article include the varying interpretation and lack of standardization that must still be overcome to achieve true global harmonization. This review also considers the next steps toward achieving simultaneous global regulatory submissions and utilizing cloud-based technology to facilitate data exchange between sponsor and regulator [6].

ICH Q12 GLOBAL IMPLEMENTATION: STATUS AND CHALLENGES

The ICH Q12 guideline provides a framework to facilitate postapproval CMC changes more predictably and efficiently through a unified risk-based approach that will benefit patients, the industry, and regulatory authorities [3, 4]. Full implementation of ICH Q12 tools across all jurisdictions may be delayed until the necessary legislative changes are made [7, 8, 10]. ICH Q12 introduces the concept of established conditions (ECs), which provides a clear understanding between the manufacturer and health authorities regarding critical manufacturing, quality, and analytical elements that require regulatory actions.

In May 2021, the US Food and Drug Administration (FDA) published a draft industry guidance, ICH Q12: Implementation Considerations for FDA-Regulated Products. This guidance complements ICH Q12 guidelines by clarifying how the ICH Q12 tools and enablers can be implemented within the US regulatory framework, and reflects critical lessons learned from the 2019 FDA Pilot Program on Established Conditions, [9, 10].

The European Medicines Agency (EMA) issued its implementation guidance in March 2020 [10]. It emphasizes that one must always default to the requirements laid down in the current European Union (EU) variations of regulation and associated guidelines [6]. Currently, the EU legal framework does not recognize the product life-cycle management (PLCM) document, which contains ECs and proposed reporting categories but does recognize PACMPs. The European Commission, together with the EMA and the National Competent Authorities, will continue to work on fully implementing the ICH Q12 guideline within the existing EU legal framework [7, 11, 12].

In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) introduced minor change notifications to the regulatory framework. However, there was no harmonization of postapproval change reporting categories across the ICH regions at the time. The application form, unique to Japan, can be the basis for using ECs to determine filing strategies for postapproval changes. Due to this unique approach, standardized global implementation of ICH Q12 has been challenging [13]. In an effort to achieve global standardization, the PMDA released a notification in March 2021 that confirms the incorporation of PACMPs into the regulatory framework, and full implementation was expected soon at the time of this writing (late 2021) [14].

At ICH Day during DIA China 2021, industry and regulatory experts agreed that real experiences from well-established regulatory systems would help China implement ICH Q12 from policy and technical perspectives. At the regulatory level, the National Medical Products Administration (NMPA) Drug Administration Law (DAL), Drug Registration Regulation (DRR), and Provisions for Post-Approval Changes have provided support for the transformation and implementation of ICH Q12 in China. The FDA has also offered both early dialogue and training to share knowledge and experience with the industry, providing an excellent example for other regulators to follow. Based on these examples, the industry in China will look to NMPA to help guide and create similar tools for effective implementation [15].

In July 2021, Health Canada (HC) released an updated draft guidance for its Post-Notice of Compliance (NOC) Changes and solicited public comments. The draft presents new guidance on what information should be submitted to HC to set ECs and proposed reporting categories, and requirements for PACMPs [16]. As part of HC's implementation of ICH's Q12 guideline, HC announced a pilot program that is specifically seeking applications and supplemental applications for biologics and pharmaceuticals that will use ECs and PACMPs [17]. HC is expected to have full implementation of ICH Q12 by late 2022 [18].

It is anticipated that even after full implementation of ICH Q12 in each region, varied health authority interpretations of the regulatory tools could lead to divergence in the approved ECs across jurisdictions, as different ECs and proposed reporting categories might be approved. Disagreement on ECs and their reporting categories could result in extended negotiations, potentially delaying review times [19]. ICH has developed additional training materials for ICH Q12 to benefit both the industry and regulators. In the future, more guidance and experiences gained through participation in pilot programs, such as the FDA EC pilot, may be necessary to clarify some of the ambiguity in identifying ECs [17]. Recent engagements between industry leads and health authorities have highlighted the value of using a standardized approach for the regulatory tools in ICH Q12 [10]. However, the long-term expectation is that the use of ICH Q12 and ECs will decrease the need for postapproval filings and regulatory agency interactions [20, 21].

Figure 1: Redundancies in the postapproval change management process contribute to delayed approval.

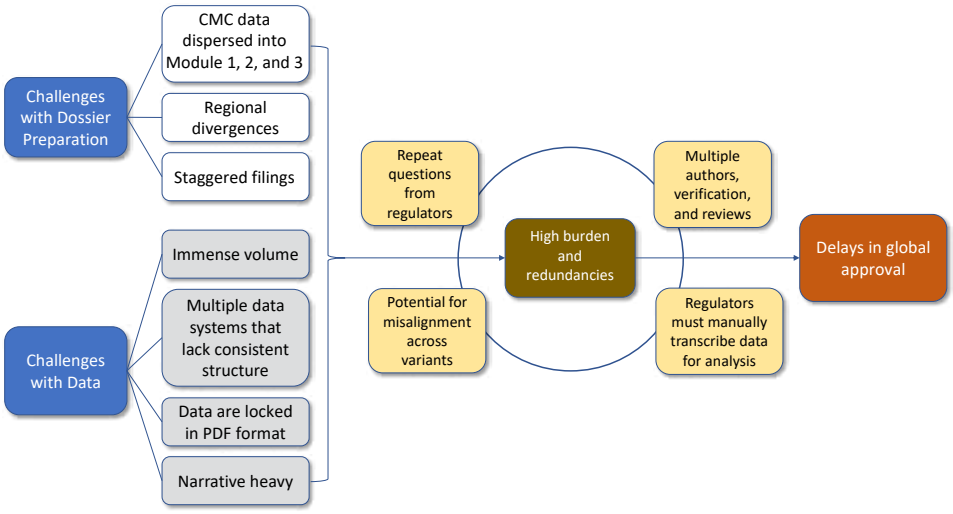
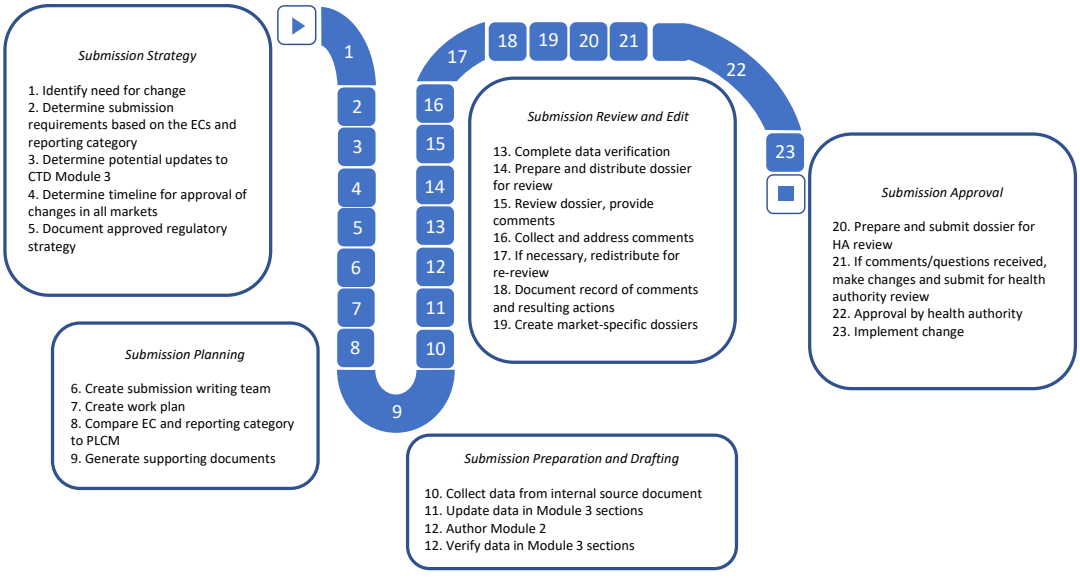


Figure 2: Current CMC postapproval submission authoring roadmap.



IMPLICATIONS FOR EXISTING PROCESSES

Delays in global approvals experienced due to lengthy CMC postapproval regulatory processes can be traced to two factors: challenges with dossier preparation and challenges with data. These challenges exist because of outdated regulatory systems and the inability to leverage state-of-the-art technology for exchange of information such as data and narratives. Collectively, challenges such as the spread of data across multiple document sections, regional differences, staggered filing timelines across markets, and the immense volume of data locked in PDF format contribute to the high burden and redundancies in postapproval regulatory submissions. The accumulation of these redundancies contributes to delays in implementation of necessary post-approval CMC changes and discourages innovation.

The current CMC authoring process for a regulatory dossier requires writing, reviewing, verifying, and approving multiple sections and subsections within Modules 1, 2, and 3 (Figures 1 and 2). This information is often spread across separate documents within a section of the module and must be manually entered, often in multiple places, before reverifying data and reapproving.

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This arduous compilation process limits the ability to compare data collected for different products and submissions. In addition, if the information provided by the sponsor requires updates or is sent to different regulators, it must be manually updated and reverified in each document in which it appears, as information is not conveniently linked across documents to enable real-time editing (Figure 1). As a result, multiple regional variants of each document must be maintained and robust tracking efforts are required to ensure that each health authority receives accurate and updated information [2].

It is similarly challenging for health authorities to provide consistent product feedback, as accessing sources, documenting prior decision-making, and review documents may also require manual work. Thus, the current submission and review process must transition from managing documents to managing data to address these challenges, remove unnecessary labor and repetition, and create more time for scientific rationale and risk-benefit analysis [5].

Numerous steps are involved in the authoring process, with the integration of ECs into the process. The postapproval change authoring process involves many stages of writing, review, and verification for large amounts of data. SCDM implementation can potentially assist with streamlining the development and verification of data necessary for these regulatory submissions.

SCDM provides the framework for authoring human- and machine-readable content by enabling an enhanced review, organization, and standardization of electronic narrative and data, allowing uniformity of approved information across documents [5]. Data automation with SCDM can potentially reduce errors and increase the accuracy of data across submissions. SCDM systems could improve the efficiency and quality of regulatory documents by establishing a standardized authoring process, mitigating risks, and decreasing time to implementation. Once the SCDM system is capable of this level of real-time data automation, the flow of existing data to finalized documents that are ready for health authority review can be established. Ideally, data and information from multiple regions could be submitted simultaneously, available for all regulatory bodies to access and review as required, thereby allowing regulators to communicate with each other and see previous questions and decisions of other regulatory bodies.

Substantial resources are required to develop and implement these advanced SCDM solutions, which has been a barrier to becoming the industry standard. SCDM could be especially useful for CMC data as it allows for creating, capturing, and reusing component information as product development progresses. Coupling the integration of ECs with the design and implementation of SCDM may increase postapproval process efficiency and enable some authoring automation. It would also ensure the ECs—which can be captured in multiple different CTD sections including Module 3 sections, Module 2 sections, and the PLCM document—are aligned [2, 3].

SCDM systems could improve the efficiency and quality of regulatory documents by establishing a standardized authoring process, mitigating risks, and decreasing time to implementation.

CASE STUDIES

Case Study 1: Potency Assay Change

Assessing potency of a drug product is a critical quality attribute of biological therapeutics [22]. Frequently, potency assays for biologics are in vitro cell-based and have complicated mechanisms of action intended to parallel that expected in vivo. Though powerful tools, cell-based bioassays can be challenging and may require remediation to increase robustness and operational need (e.g., risk mitigation of critical reagents/instruments). It is a complex task to implement a modification to a potency assay across different regions as prior regulatory approval would typically be required.

In this case study, a company is interested in optimizing a potency assay for a therapeutic monoclonal antibody approved in 50 countries to decrease the rate of invalid test results. As part of the change management process, personnel must manually find, view, and interpret the older data sets to establish a frame of reference for completing method validation exercises and compare the initial and optimized assays. Following data collection, the authoring and submission process begins as described in Figure 2, which could take a minimum of three months to complete. Testing with both potency assay methods, pre- and post-change, is necessary to gain approval from health authorities, resulting in two sets of data to be collected and submitted to each health authority.

As the product has an extensive global footprint, full approval for the change across all jurisdictions could take as long as five to six years. During this time, duplicate testing with both potency assay methods would be necessary, resulting in a significant cost burden to the sponsor. Incorporating ECs into this case study, when agreed upon with the regulator, can potentially lower the reporting category of the change, thereby reducing the timeline for approval (Figure 3). The use of a PACMP may be another option where similar timelines may be achieved. As a result, in this example, the applicant might implement the new potency assay method after 30 days for the US (CBE-30) and report the change to global health authorities afterwards in a more structured timeframe. Providing data in a usable SCDM format through a cloud-based

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- Procurement Assistance
- GMP Review
- Site Master Plan

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- Medical Device Compliance
- Trainings & Auditing services

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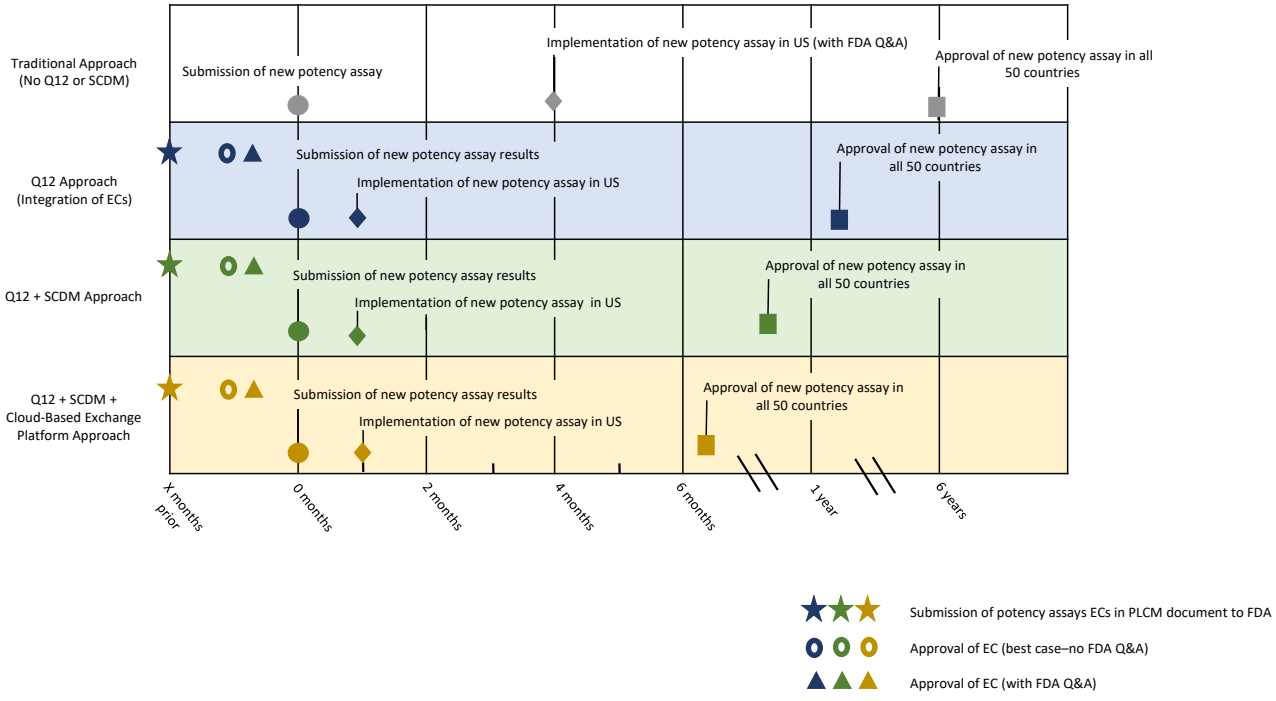
Figure 3: Theoretical reduction in time to global approval with implementation of Q12, SCDM, and cloud-based exchange.



ecosystem would have the potential to enhance data analysis, further improve global filing and review efficiencies, and shorten the overall time to global approval.

The first row of the timeline (white) displays the approach taken without incorporating ECs or SCDM. The second row (blue) demonstrates how the use of ECs can lower the reporting category. The third row (green) demonstrates the shortened time to global approval that can be achieved by incorporating both ECs and SCDM.

Additional efficiencies and further reduction in time to global approval are possible by leveraging a cloud-based filing and review platform (fourth row, yellow) [10]. For example, two large data sets could be automatically imported into regulatory documents without manually transcribing and locking data in PDF format. The use of ECs can streamline the postapproval process by potentially reducing the reporting category of the change, while SCDM may increase the efficiency and automation of document generation for submission to multiple countries. The use of both ECs and SCDM could thus shorten the timeline for global change approval and implementation.

Case Study 2: Alternate Sterile Filter to Address Shortage

Filter shortages across the industry due to the COVID-19 pandemic are driving the need to rapidly qualify new filters from alternate vendors. All filters used in the manufacture of a product must be characterized by the pharmaceutical quality system (PQS). The characterization data need to demonstrate that the filters are equivalent, with no impact to bacterial retention, product binding, or the extractables/leachable risk profile.

According to existing guidance, prior approval is required to implement an alternate filter in most markets. Due to varying regulations and long approval timelines, global implementation of an alternate filter may lead to delays in implementation, and potentially lead to drug shortages.

Due to the nature of the change and potential impact to product quality, and per a sponsor's internal PQS, process validation data are required to support a filter change. In this case study, the sponsor submits a PACMP to a health authority. The PACMP contains small-scale characterization data for the alternate filter, with a commitment to provide at-scale data in subsequent annual reports. The filter validation acceptance criteria are ECs in the previously approved PLCM.

In this scenario, if the sponsor has an approved global PLCM document describing the ECs with a reduced reporting category, the time required to implement the alternate filter can be reduced. Identical submissions are created with the same viral filter load in-process controls (IPCs) and submitted to all regions with a reduced filing category and overall implementation timeline. However, information requests from various health authorities invariably lead to additional country-specific variants containing different acceptable ranges for viral filter load IPC, thus creating multiple variants of Module 3 sections and PLCM documents.

The use of SCDM in this case study could allow data from

previous filter characterization studies, including cleaning validation, viral clearance, and extractables/leachables to be better tracked to improve efficiency of the authoring process. Filing preparation would be simplified, as data would not have to be manually transcribed and verified, saving on submission authoring time. When information requests from various health authorities are received, filing automation would allow efficient updates to Module 2, Module 3, and the PLCM document. Thus, use of ECs together with incorporation of SCDM concepts would shorten the timeline for change implementation, thus de-risking potential impact on patient supply.

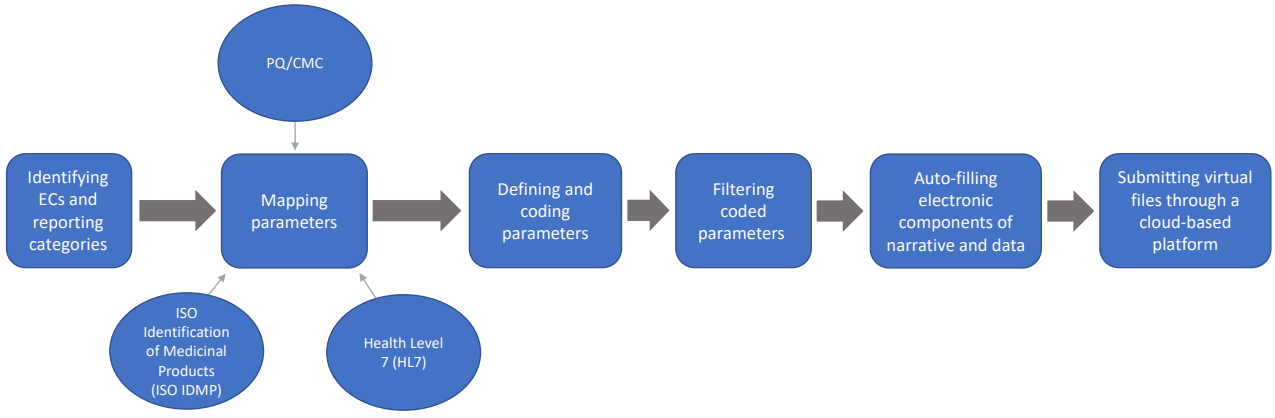
Case Study 3: Trypsin Reagent Replacement for Peptide Map Method

Routine method revisions enhance method performance and mitigate critical reagent supply. In this theoretical case study, the sponsor must replace the trypsin reagent used in the peptide map method due to a raw material shortage. The sponsor is required to evaluate an alternate manufacturer for trypsin and to characterize the new trypsin (from the same source) [23], which is then qualified, confirmed equivalent to the previous trypsin, and deemed acceptable for use. Execution of the peptide map method does not change in response to the new trypsin that is filed globally; however, some regions may require prior approval to implement this change. The sponsor incurs unnecessary expenditures by making this change because they must run peptide map testing twice, using both the old and the new trypsin, until global implementation of the change can be achieved. The sponsor also runs the risk of running out of stock of the currently approved trypsin, potentially leading to a supply risk in countries where the change has not been approved.

Using ICH Q12 principles, the peptide map method would be filed with an accompanying PLCM document in which any low-risk change to raw materials in a method is defined as an EC with a "notification low" reporting category, meaning the change would not require approval or notification prior to implementation. The required qualification data justifies the lower reporting category. With prior regulator agreement, this method reagent change can then be implemented as a notification low/annual reportable change with reduced reporting categories worldwide. The sponsor can implement the new trypsin immediately in drug substance/drug product (DS/DP) release testing with one peptide map method, eliminating costs associated with redundant testing. The old method can be replaced immediately, and duplicate testing would not be required.

However, the sponsor is still required to author the submission and submit the data for the peptide map raw material change to each region. As described earlier, creation of individual

Figure 4: Potential collaboration between ICH Q12 and SCDM, and FDA CBER-CDER data standards strategy to streamline CMC submissions.



submissions for each region, including country-specific variants, is a resource-intensive process. The overall time required to author and submit the trypsin reagent change could be reduced by leveraging both ICH Q12 tools as well as SCDM and authoring automation.

Use of ICH Q12 methodology would lower the reporting requirements, allowing for quicker implementation of the change. SCDM would decrease resources and time needed to manually transcribe and verify data in a CTD section. SCDM would also allow for rapid exchange of additional data if health authority reviewers needed it to support review.

FUTURE CONSIDERATIONS

During the COVID-19 pandemic, it has become apparent that the pharmaceutical industry can rapidly adapt in response to public health emergencies. The fragile nature of the pharmaceutical supply chain became apparent, demonstrating the need for manufacturing flexibility for existing products. The rapid transition between clinical studies to emergency use authorization, and then to the world's first fully approved vaccine in under two years, highlights the potential of biopharmaceutical companies and health authorities. On the basis of medical need, science-driven risk, and the need for manufacturing flexibility and efficiency, similar acceleration of regulatory approvals could potentially be achieved for any life-saving medication. The technology now exists for information and data exchange within the postapproval space to match the speed of product drug development and innovation.

To meet the challenges in the existing CMC regulatory landscape, standardization and harmonization of ICH Q12 regulatory tools across different regions (including non-ICH regions) would be needed. In addition, significant regulatory reform, and modernization, including digitalization and digitization, would be necessary to achieve a single standardized global submission. At the FDA, the Technology Modernization Action Plan (TMAP) and the Data Modernization Action Plan (DMAP) aim to modernize its digital infrastructure [24]. The FDA has recently announced the reorganization of the agency's information technology (IT), data management, and cybersecurity functions into the new Office of Digital Transformation (ODT). The ODT allows more effective data management to streamline operations by reducing duplicative processes and implementing technological efficiencies [25].

The flowchart in Figure 4 shows the overlap and proposed workflow after both the sponsor and the health authority implement ECs; SCDM; identified and mapped data parameters based upon FDA PQ/CMC (pharmaceutical quality/chemistry, manufacturing, and control) information; and universal standards, such as International Organization for Standardization (ISO) Identification of Medicinal Products (IDMP) and Health Level 7 (HL7) standards.

With the implementation of ECs and SCDM, sponsors could standardize and simplify their internal documentation while maintaining alignment with the externally standardized regulatory requirements. In that case, data and information can be further coded and standardized into an online, cloud-based data exchange platform that can facilitate automatic updates [26–28].

The FDA's Center for Biologics Evaluation and Research (CBER)/Center for Drug Evaluation and Research (CDER) Data Standards Plan is an ongoing project that aims to map PQ/CMC data elements, standardizing application content to facilitate efficient risk-based reviews by linking data and common categories and elements across various application types. A secondary goal of this project is to provide recommendations for standardization of the categories and elements necessary for application review. Where corresponding data elements exist, the identified PQ/CMC data parameters overlap and, in some instances, directly align with the substance and product identifiers described by the ISO IDMP standards (Figure 4). After the identification and standardized mapping of these data parameters, they are submitted to the ICH CTD [24, 29]. The longer term goals of this project are to increasingly replace dossiers with structured content and data

supporting dossier variations with more efficient online database updates [28].

The need for a more templated and structured approach to the sections within Module 3 is clear. Revision of ICH M4Q has commenced with endorsement of the concept paper in November 2021, to be followed by an ICH topic proposal on structured product quality submissions [23]. Both ECs and SCDM facilitate standardized language across regions, and this language can align with mapped data parameters using PQ/CMC, ISO IDMP, and HL7 standards and Fast Healthcare Interoperability Resources (FHIR) artifacts. The collaboration between these tools can allow sponsors to store structured information to potentially be used as a single global submission that is consistent, reproducible, and easily accessible by health authorities across different regions [24, 29, 30].

To achieve the goal of a single global submission, up-to-date information must be exchanged seamlessly between sponsors and regulators. Accumulus Synergy, a nonprofit sponsored by leading biopharmaceutical companies, is developing a cloud-based platform intended to facilitate real-time data exchange and review in a worldwide setting. The platform under development proposes locked and shared spaces in the cloud, allowing both sponsors and regulators to work and communicate with each other across portals and protected by firewalls. Sponsors could use SCDM systems to automate the compilation of data and electronic narrative and push this information to the Accumulus cloud to facilitate efficient data exchange, collaboration, and parallel reviews, thus improving the submission and review process.

In addition to ease of access and exchange of information, reviewing regulatory submissions in parallel can reduce the total time to approval for a drug product in multiple regions. Providing a platform by which data can be exchanged in usable format enables more efficient filing processing and improved assessment capabilities. Once the principles of data exchange automation are established, they can be extended to clinical, preclinical, and summary data [6].

CONCLUSION

There is a perception that once a product is commercialized, or a marketing application is approved, that the work associated with product filings is complete. On the contrary, the work is essentially only beginning from a CMC perspective because the product is optimized multiple times and in many areas over the lifetime of its commercial viability. Several challenges burden the current global regulatory submission workflow for postapproval CMC changes. There is a need for efficiency and consistency within the postapproval regulatory space to reduce the high costs, complicated surveillance of updated regulatory requirements, and management of the large volumes of data that accompany CMC changes.

The use of regulatory tools, namely ECs as described in the ICH Q12 guideline, provides a unified and flexible approach in reporting postapproval changes to health authorities, and an avenue for more efficient change implementation. Combining ECs with an SCDM system may enable automated authoring of human- and machine-readable content supporting an enhanced review, structured organization, and standardization of documents submitted to health authorities in line with the PCLM. With the varying interpretation of the ICH Q12 guideline by sponsors and health authorities, efforts must be made to enhance standardization and harmonization. As a complement to the initiatives taken by the FDA, SCDM could be an efficient solution to address challenges in the current CMC regulatory submission and review process. Combining the benefits of ICH Q12 and SCDM with a cloud-based filing and review ecosystem could propel the pharmaceutical industry digitally forward to deliver therapies more effectively and efficiently to patients around the world in a timelier manner. These concepts and platforms can subsequently be leveraged to expand beyond CMC data and attain a single global regulatory submission for new drug applications including non-clinical, clinical, and safety modules.

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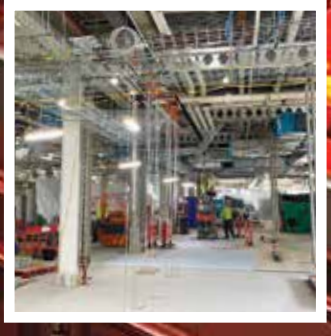

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REGULATORY LANDSCAPE FOR RAW MATERIALS:

CMC Considerations

By Jacqueline E. Milne, PhD, Nina S. Cauchon, PhD, Jill Beierle, MS, Amy C. Rhee, MS, Tabetha M. Bonacci, PhD, Ailsa Surman, Andrew C. Lennard, PhD, John K. Mark, William Garden, and Susan E. Burke, PhD

A reliable supply of raw materials is critical to maintain a robust supply chain to serve patients globally. With shortages, regulatory complexity is compounded due to differences in submission and data requirements from various regulatory agencies. Therefore, there is an increasing need to implement a harmonized regulatory infrastructure that is both flexible and predictable to provide more agility without product delays.

The pharmaceutical manufacturing supply chain starts with the raw materials, which are needed to ensure drug availability for patients. With ever-increasing supply chain challenges, raw material shortages have become a point of discussion. In this article, the term "raw material" refers to a material used in the manufacturing and packaging of a drug substance (DS) or a drug product (DP).

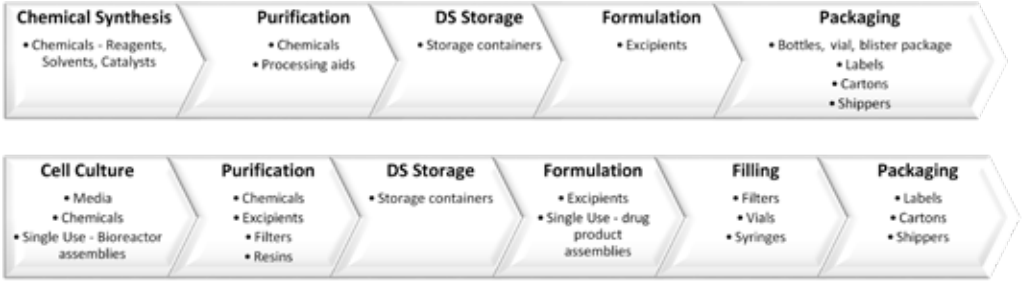
For a synthetic drug, the DS is chemically synthesized in multiple ordered steps from the starting materials using a range of chemicals. This is followed by DP manufacturing, where the DS is formulated with excipients. Finally, the DP is packaged in a suitable container to ensure continued quality.

For a biologic drug, the DS is manufactured upstream in cell culture media followed by downstream purification, which requires chemicals, filters, and resins. The DP formulation and filling processes use excipients, filters, vials, and syringes. In addition, single-use technologies have been increasingly employed throughout manufacturing because of the advantages they offer, including reductions in cost, manufacturing footprint, contamination risk, and processing times (Figure 1).

Although they have been historically overlooked as a key element, raw materials are a critical component at every stage of the drug manufacturing processes. Recent US FDA data show that the lack of raw material availability contributes to 27% of drug shortages (see Appendix, https://ispe.org/appendix_regulatory_landscape_sept-oct_2022_pe).

There is undoubtedly a need for improved supply chain flexibility to address shortages. In cases where raw materials are single

Figure 1: Raw materials in synthetics and biologics processes.



sourced, supplier manufacturing problems or product facility closures could result in manufacturing delays and/or stoppages. Similarly, an increased demand forecast could lead to a raw material shortage. One possible mitigation strategy is to build sufficient inventory to ensure continuous product supply. However, large inventories increase the cost of production and the risk of scrapping raw material lots that exceed their shelf life before they can be used.

Diversification and redundancy of raw material supplies by qualification of new raw material sources ensure a geographic footprint of manufacturers providing flexibility and supply resiliency. However, use of alternative raw materials may require approvals from multiple health authorities. Waiting for approvals can significantly delay implementing a change, and the timelines vary between regions, adding further complexity to supply management. For example, implementation of an alternative vial would typically require 4 to 6 months for approval in the EU and US but more than 18 months in other countries. In some cases, to meet the forecast, DP manufacturers manufacture at risk while waiting for approvals for second-source supply.

During the pandemic, the pharmaceutical industry faced challenges in the production of COVID-19 therapeutics and vaccines to meet global demand, as well as mitigation of drug shortages for non-COVID-19-related products, without compromising product quality or patient safety. Lessons learned during the pandemic could be leveraged for future procedures and regulatory submission requirements. This article highlights the regulatory expectations of raw materials, the challenges of postapproval changes. and the impact on supply resiliency. Case studies are presented that demonstrate the importance of defining the raw material attributes that are critical to product quality and how this could support increased postapproval flexibility (including the use of ICH Q12 principles).

REGULATORY EXPECTATIONS

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines contain information regarding regulatory requirements for raw materials. There should be a system for evaluating critical suppliers and a specification agreed upon with the supplier and approved by quality. Upon receipt, incoming raw materials should be tested against specifications that include critical attributes, analytical procedures, and acceptance criteria. Additional requirements are described in ICH Q7 [1]. The Common Technical Document (CTD) for the Registration of Pharmaceuticals For Human Use: Quality—M4Q guidance covers the minimum requirements for submission of raw materials; however, certain regions have additional requirements [2].

Raw materials used in the manufacture of the DS should be listed in CTD section 3.2.S.2.3, Control of Materials. The name of each material, where it is used in the process, and information on the quality and control should be provided. The material manufacturer is not required for all cases but is often requested by some health authorities for critical materials such as filters. A compendial or multicompendial grade should be listed where applicable; for all noncompendial materials, specifications should be included. Information demonstrating that the quality of the raw materials meets standards appropriate for their intended use should be provided. For example, biologically sourced raw materials may require careful evaluation to establish the presence or absence of deleterious endogenous or adventitious agents.

Per ICH Q11, the potential for material attributes that impact DS critical quality attributes should be identified [3]. Raw materials used near the end of the manufacturing process have greater potential to introduce impurities into the DS than raw materials used upstream; therefore, tighter control of quality should be evaluated. A risk assessment to define the control strategy of raw materials can include an assessment of manufacturing process capability, attribute detectability, and severity of impact. For example, the ability of the DS manufacturing process to remove an impurity or limitations in detectability (e.g., viral safety) should be considered. The risk related to impurities is typically controlled either by raw material specifications or robust purification steps later in the synthesis.

An excipient is formulated with the active pharmaceutical ingredient and is typically not chemically or physically altered prior to use; therefore, all components are likely present in the DP. The intended end use of the excipient should be considered when determining the appropriate regulatory and GMP requirements for the excipient and its manufacturing facility. The quality of the excipients and the container/closure systems should meet pharmacopeial standards, where available and appropriate. Otherwise, suitable acceptance criteria should be established. The use of a noncompendial material may be considered acceptable with strong scientific justification. For a multicompendial excipient that may be marketed for global use, the DP manufacturer should demonstrate conformance of the excipient to the monograph requirements found in specified compendia.

A description of the DP and its composition is provided in CTD section 3.2.P.1, Description and Composition of the Drug Product. More details regarding the quality of excipients are provided in CTD section 3.2.P.4, Control of Excipients. For the European Medicines Agency (EMA), functional related attributes should also be considered, and it may be necessary to include additional tests and acceptance criteria, depending on the intended use of the excipient (see Appendix). For excipients of human or animal origin, information should be provided regarding adventitious agents in CTD section 3.2.A.2, Adventitious Agents Safety Evaluation. For novel excipients (i.e., excipients used for the first time in a DP or by a new route of administration), full details of manufacture, characterization, and controls, with cross-references to supporting safety data, should be provided according to the DS format in CTD section 3.2.A.3, Novel Excipients [4].

Additionally, excipients and primary container components may be subject to regional regulatory requirements. For example, the National Medical Products Administration (NMPA) requires

registration of high-risk excipients and primary container components using a master file that is referenced by the DP sponsor.

POSTAPPROVAL CHANGE MANAGEMENT

When a drug manufacturer intends to introduce a change, the potential impact on the process and product quality must be assessed [1, 5, 6]. A change is classified as major, moderate, or minor depending on its nature and impact. A major change is one that requires submission and approval by a health authority prior to distribution of post-change material. A moderate change is one that typically requires submission to a health authority but may not require approval prior to distribution of post-change material. A minor change is reported to the health authority after implementation and does not require a submission prior to product distribution. The classification helps determine the data required to demonstrate comparability (pre- and post-change) and confirm no adverse impact on product quality.

A formal change control system under the company's pharmaceutical quality system (PQS) is required to evaluate all raw material changes, with established procedures for identification, documentation, review, and approval. A quality risk management system provides assurance to the health authorities that the applicant can ensure process consistency and product quality while continuously monitoring, verifying, and mitigating identified risks. After approval and implementation of the change, there should be an evaluation of the first batches produced post-change.

Health authorities have divergent classifications for changes in terms of risk to product quality and documentation/data requirements. Table 1 shows the classifications assigned (based on published guidance) to three distinct types of raw material changes for biologics (B) and synthetics (S) across six regulators (FDA, EMA, Health Canada, Therapeutic Goods Administration [TGA], Pharmaceuticals and Medical Devices Agency [PMDA], and NMPA) and the World Health Organization (WHO):

- Relaxing acceptance criteria or deleting a test for a raw material. Although this change is not explicitly described in the TGA guidance, a change category requires that any change to raw material specifications be submitted as a Category 3 application requiring prior approval. The PMDA classifies such a change as a partial change application requiring prior approval if the acceptance criteria or test is registered in M1.2. It is considered a moderate change by the FDA (CBE30) and NMPA. In the EMA, Health Canada, and WHO, such a change would be considered minor, provided the deleted parameter was redundant or obsolete. In the case of deletion of an attribute specification that may have a significant effect on product quality, the EMA classifies it as a major type II variation requiring approval before implementation. Health Canada classifies this type of change as level 2 for biologics, which requires approval prior to implementation, or level 3, which requires immediate notification for synthetics, which allows implementation prior to reporting to the agency.
- Relaxing acceptance criteria for compendial excipients to comply with changes to compendia. This change ranges from a moderate change (CBE-30) by the FDA to a minor change not requiring prior approval by the WHO.
- Change to manufacturer or supplier of excipients or raw materials. Classifications vary widely by region depending on the raw material involved and route of administration. Consistently a change in the source of an excipient to one that carries a risk for transmissible spongiform encephalopathy (TSE) is considered a major change. This classification can be reduced to a minor change according to Health Canada and the WHO if supported by a valid TSE Certificate of Suitability (CEP).

Some health authorities do not include all three changes described in their postapproval guidance; for example, the FDA provides guidance for synthetics, but not biologics. Changes not covered need case-by-case management. In addition, submission categories vary between health authorities, making it very challenging to manage the submissions for a raw material change globally. In some guidance documents, changes require associated conditions to be met and documentation/data to be provided in a specified submission category. If a condition cannot be met, then the submission category may be upgraded to a higher category.

Additional examples of postapproval changes for FDA, EMA, Health Canada, TGA, PMDA, NMPA, and WHO are described in detail in the Appendix. The categories in the Appendix assume all conditions are met, required documentation is available for submission, and they are aligned with health agency expectations. The absence of any of the listed documentation should be scientifically justified.

Due to global regulatory requirements, many postapproval changes cannot be implemented until the health authorities have reviewed and approved the change, which can take considerable time. During technical review, additional time and resources may be required to address requests for information from agencies. Because of the lack of harmonization across regions, it is difficult to predict the time that it will take for approval by each health authority. The estimated global approval times for major changes vary considerably—from less than 6 months in some major markets to greater than 18 months in others—resulting in periods of several years before full global implementation of a change can occur [7].

This results in a lack of supply chain agility to implement changes when faced with immediate supply shortages. Managing a strategy to accommodate varying global approval timelines is a challenge. Similarly, there are regulatory hurdles to implementing raw material improvements postapproval to proactively improve raw material reliability (e.g., innovative technologies and raw material specification changes enabled through scientific understanding of raw material attributes and their impact on product quality).

ADDRESSING CHALLENGES FOR POSTAPPROVAL CHANGES

Multiple asynchronous reviews of the same information with varying approval timelines across global health authorities

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Table 1: Comparison of the submission category of three types of raw material changes for synthetics (S) and biologics (B).

Health authorities	Relaxing acceptance criteria or deleting a test for a raw material	Relaxing acceptance criteria for compendial excipients to comply with changes to compendia	Change to manufacturer or supplier of excipients or raw materials
FDA	Moderate CBE-30 • Relaxing acceptance criteria or deleting a test for raw materials used in drug substance manufacturing (except raw material testing for viruses or adventitious agents which would be prior approval) (S)	Moderate: CBE-30 • Relaxation of acceptance criteria or deleting a test to comply with an official compendium (S)	Annual Report • A change in excipient supplier, where the technical grade and specification remain the same (S)
EMA	Major Type II • Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product (B) (S) Moderate Type 1B • Deletion of a non-significant specification parameter (e.g., deletion of an obsolete parameter) (B) Minor Type IA • Deletion of a non-significant specification parameter (e.g., deletion of an obsolete parameter) (S)		Major Type II • Change to manufacturer of a reagent that uses a substantially different synthetic route or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability (B) (S) • Change in source or introduction of an excipient or reagent with TSE risk (B) (S) Minor Type 1B • Change in source of excipient or reagent from TSE risk material to vegetable or synthetic (used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product) (B) (S) Minor 1A • Change in source of excipient or reagent from TSE risk material to vegetable or synthetic (not used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product) (B) (S)
TGA	Category 3 • Any proposed changes to the specifications of the excipients, raw materials can be submitted as Category 3 (S). No specific guidance regarding relaxing acceptance criteria or deleting a test **Note:** Narrowing of limits/more stringent of an excipient is a notification (S)	Notification • Amendments to excipient specification resulting from pharmacopeial change (B) (S)	Category 3 • Change to source or method of manufacture of raw materials and excipients of human and animal origin (B) • Changes to source or method of manufacture of excipients of animal origin (S) Self-Reportable • Excipient's manufacture (from Category IC ruminant tissues, defined as TSE)–changes in source (from animal to non-animal) and/or manufacturing process or site (B) • Change to manufacturer or supplier of excipients or raw materials (not to materials of animal or human origin) (B) Notifications • Changes to the source, manufacturing process, or site of manufacture of excipients derived from Category IC ruminant tissues, including from animal to plant or non-animal source. The product must only be intended for oral, topical, vaginal, rectal, or inhalation routes, with no potential for cross-contamination with higher risk (Category A or B) tissues (S) No Prior Approval • Change to local handling agent/distributer contact details of an excipient (no reporting requirement) (B) (S) • Changes to the manufacturing process and site of manufacture of excipients of the same specifications (excluding excipients of animal or human origin) (S) **Note:** Category IC–no detectable infectivity; Category A–sourced from region with negligible BSE risk; and Category B–sourced from region with controlled BSE risk

table continues

Table 1 continued

Health authorities	Relaxing acceptance criteria or deleting a test for a raw material	Relaxing acceptance criteria for compendial excipients to comply with changes to compendia	Change to manufacturer or supplier of excipients or raw materials
Health Canada	Level 2 Notifiable Change • Changes in critical controls for the raw materials (e.g., solvents, reagents, catalysts, processing aids) (B) Level 3 Immediate Notification • Changes in critical controls for the raw materials (e.g., solvents, reagents, catalysts, processing aids) (S) Level 3 Annual Notification (Minor) • Minor changes to specifications for noncritical materials that are discrete chemical entities (e.g., raw materials, solvents, reagents, catalysts)–no changes to DS specifications or impurity profile, does not affect sterilization procedures of a sterile DS (S) • Deletion of a specification test used to release the excipient, demonstrated to be redundant or is no longer a pharmacopeial requirement (B) **Note:** Change in specification of solvents, reagents, catalysts to either the same or higher quality and not impacting impurity profile of DS or its specification outside of approved limits is annual notification (B)	Level 3 Annual Notification (Minor) • Relaxation of an acceptance criterion used to release the excipient provided class 3 residual solvents is within ICH limits (a deleted test is demonstrated to be redundant/no longer pharmacopeial requirement and doesn't affect functional properties of excipient or drug product performance) (B) • Change in the standard/monograph (i.e., specifications) claimed for the excipient—no change to functional properties outside approved ranges, no deletion of tests or relaxation of acceptance criteria except to comply with monograph (B) • Minor changes in the specifications used to release the excipient–to an approved analytical procedure or reflect a pharmacopeial update (B) **Note:** Change in specifications for a compendial raw material to comply with an updated pharmacopeial standard/monograph is Level 4: Not reported (B)	Level 1 Supplement (Major) • Change in the source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a TSE or viral risk (B) (S) • Change in the source of an excipient from one TSE risk (i.e., animal) source to a different TSE risk (i.e., animal) source (S) • Change in manufacture of a biological excipient (B) Notifiable Change • Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source that does not concern a human plasma–derived excipient (B) Level 3 Annual Notification (Minor) • Change in the source of an excipient from a TSE risk (e.g., animal) to a different TSE risk (e.g., animal source) that is supported by a valid TSE Certificate of Suitability (CEP) and is of the same or lower TSE risk, does not require assessment of viral safety, and does not concern human plasma-derived excipient (B) • Change in the source of an excipient from a vegetable source, synthetic source, or non-TSE risk (i.e., animal) source to a TSE risk (i.e., animal) source; or a TSE risk (e.g., animal) to a different TSE risk (e.g., animal source) does not involve qualitative or quantitative change in excipient. The change of source is supported by a valid Transmissible Spongiform Encephalopathy (TSE) Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM) or excipient is obtained from a previously approved source (S) • Change in the source of an excipient from a TSE risk (e.g., animal) source to a vegetable or synthetic source (S) • Change in supplier of an excipient of nonbiological origin or of biological origin (excluding human plasma-derived excipient) provided no change in the specifications of the excipient or drug product outside of the approved ranges and the excipient does not influence the structure/conformation of the active ingredient (B)
PMDA	Partial Change Application • If acceptance criteria or a test for a raw material is registered in M1.2, both changes are major (PCA) and require prior approval. If not, it is not reportable (S) (B)	No Impact • If relaxation of acceptance criteria for compendial excipients to comply with changes to compendia, it is not reportable (S) (B)	No Impact • Manufacturer or supplier of excipients or raw materials is not registered in M1.2 (S) (B)

table continues

result in a more complex supply chain, without improving safety, quality, or efficacy. Currently, a streamlined data package for fast global implementation of a change is unlikely to be accepted due to differing regional data requirements.

The implementation of a global regulatory infrastructure that is harmonized, flexible, and predictable would provide drug manufacturers the agility to expedite raw material supplier qualifications to be better equipped to face raw material challenges while maintaining product quality and supply to patients. The identification of the critical raw material attributes and appropriate setting of specifications is a crucial first step.

Attribute-focused Approach to Developing Material Specifications

A robust raw material control strategy can be achieved with an attribute-focused approach to identify critical material attributes. This approach facilitates the development of science-based raw material specifications and phase-appropriate decisions across the life cycle of a material. It is important to engage in material attribute understanding early in commercial process development when raw materials are being selected. A well-defined material target profile can be used to conduct a material attribute assessment, and based on that profile, a control assessment can be completed. This can be executed in several stages:

Table 1 continued

Health authorities	Relaxing acceptance criteria or deleting a test for a raw material	Relaxing acceptance criteria for compendial excipients to comply with changes to compendia	Change to manufacturer or supplier of excipients or raw materials
NMPA	Moderate • Reduction in test item/ relaxation of specification criteria (B) **Note:** Changing the specification of an excipient where the quality control level is not lowered is also moderate (S) except when tightening quality control limits is a minor change (S). In comparison, addition of test item or tightening of limit of specification is moderate for biologics (B)	Not described in the guidance	Major • Source change for materials of animal origin (B) • Addition/ replacement of excipient supplier (B) Moderate • Source change for materials of animal origin. Critical quality attributes of products are not influenced. Replace to non-animal-derived materials, such as tissue or plasma-derived raw materials are changed to recombinant products and animal-derived raw materials are replaced to plant-derived raw materials (B) • Addition/replacement of excipient supplier–Safety level and specification requirements of excipients after change are not lower than the current excipients. The stability and efficacy of drug product are not reduced after changing excipients. Excipient suppliers are approved pharmaceutical Excipient suppliers, or registered suppliers in Category A (B) Minor • Changing the supplier of an excipient where the technical grade of the excipient is unchanged and the quality of the excipient is not downgraded (S) • Source change for materials of animal origin. Critical quality attributes of products are not influenced and the replacement is for compendial animal-derived raw materials, e.g., newborn calf serum (B) • Addition/replacement of excipient supplier–Safety level and specification requirements of excipients after change are not lower than the current excipients. The stability and efficacy of drug product are not reduced after changing excipients. Excipient suppliers are approved pharmaceutical excipient suppliers, or registered suppliers in category A. Excipients such as inorganic salt and sucrose with simple preparation and stable physical and chemical properties will not cause changes in the formulation of the final drug product (B) **Note:** Category A–If the application for registration of a drug product bundles with the registered API, excipients and packing materials, when the drug product is approved, it indicates that the bundling of API, excipients, and packing materials has passed the technical review and will be identified as "A" on the registration platform
WHO	Minor Quality Change • Deletion of a test used to release an excipient (test demonstrated to be redundant or is no longer a pharmacopeial requirement) (B)	No Impact • Change in specifications for a compendial raw material, a compendial excipient or a compendial container closure component to comply with an updated pharmacopoeia standard/ monograph (B)	Major Quality Change • Change in the source of an excipient from a vegetable or synthetic source to a human or animal source that may pose a TSE or viral risk (B) Moderate Quality Change • Change in the source of an excipient from a TSE risk (for example, animal) source to a vegetable or synthetic source (B) Minor Quality Change • Replacement in the source of an excipient from a TSE risk source to a different TSE risk source (for example, different animal source, different country of origin). The TSE risk source is covered by a TSE certificate of suitability and is of the same or lower TSE risk as the previously approved material (B) • Change in manufacture of a biological excipient that is not a human plasma derived excipient and there is no change to the specification of the excipient or drug product outside the approved limits (B)

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- Define the role of the raw material. Determine how it will be used in the process and what functions it needs to perform its intended use.
- Assess the attributes that the raw material requires to perform the desired function and identify the critical material attributes that impact the process performance and product quality.
- Define the desired target and allowable range for each material attribute based on the knowledge and understanding of the process tolerance.
- Build a control strategy to define the material attribute controls required, from the raw material manufacturing to the receipt and testing at the drug manufacturer.

The attribute-focused approach enables identifying critical material attributes and developing science-based specifications, which are established based on the intended use of the material and the process requirements; for example, avoiding the use of compendial-grade specifications when noncompendial material will suffice or avoiding the use of technical-grade raw materials when more control is required. In addition, having clear user requirements facilitates more informed supplier selection and can support the identification of established conditions (ECs) for raw materials in regulatory filings.

Once the critical material attributes have been established, specifications defined, and suppliers onboarded through the pharmaceutical manufacturer's quality management system, raw material performance can be monitored using attribute data analytics. This enables the predictive assessment of raw material variation, identification of the source of variability, and implementation of proactive mitigations strategies to prevent failures [7].

Regulatory submissions preferably include only the critical material attributes. For postapproval raw material changes, the material target attribute profile can facilitate a strong scientific justification based on the knowledge and understanding of the process and the critical material attributes. Some examples of noncritical details include registering trade names, listing part/catalog numbers, and information included in the supplier certificate of analysis that is not relevant to ensure product quality. Registration of these details may limit options of second sourcing, especially in the worst-case scenario when a supplier discontinues a material.

Utilization of Regulatory Tools in ICH Q12

ICH Q12 helps streamline postapproval change implementation by establishing harmonized change categorization, including the identification of the portions of an application requiring a submission if changed postapproval [8]. The level of submission category for a change is determined by the level of risk associated with making the change. ICH Q12 provides a framework to enable the modification of some submission categories for changes based on scientific understanding and the level of risk associated with the change.

It includes regulatory tools such as ECs, postapproval change management protocols, and the product life-cycle management document to enhance the manufacturer's ability to manage chemistry, manufacturing, and controls (CMC) changes effectively under the company's PQS [9]. Adoption of the principles of ICH Q12 could result in fewer postapproval submissions and the ability to implement more changes prior to notification.

According to ICH Q12, "ECs are legally binding information" within an application considered necessary to assure product quality. Any change to an EC requires a submission to the health authority. Identifying ECs enables a risk-based framework, allowing the use of scientific knowledge and risk mitigation to justify the submission category of a change.

The number of ECs for a raw material, how narrowly they are defined, and the associated submission category depend on several factors:

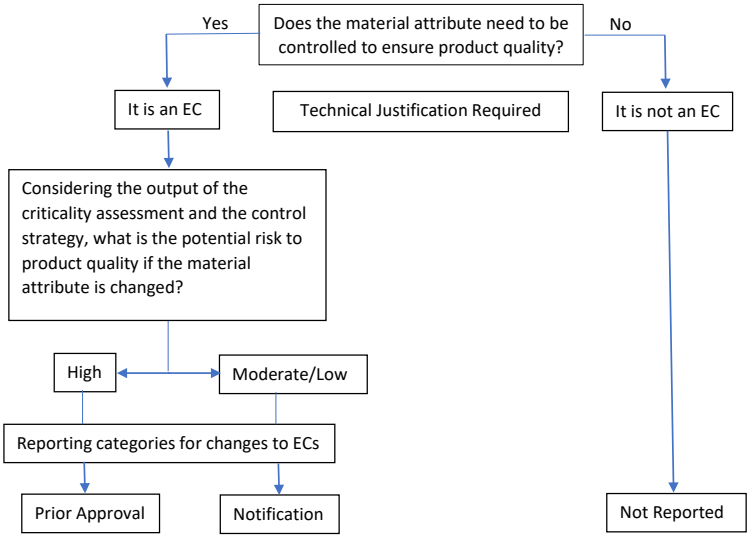
- Characterization of the product and detection limits of product quality attributes: Development approach adopted, which dictates the level of process and product quality understanding.
- Performance based: High level of scientific understanding of the material attributes that have an impact on process performance and product quality. Data-driven enhanced control strategy primarily focused on the control of process outputs and an improved understanding of the risk.
- Parameter based: Limited understanding of relationship between inputs and resulting product quality attributes. A larger number of material attributes are considered potentially critical.
- The potential risk to product quality when implementing changes to the EC: Risk assessment activities should follow approaches described in ICH Q9 and must consider the overall control strategy and any possible concurrent changes [10].

In general, enhanced knowledge and understanding of the relationship between raw material attributes, process parameters, and product quality enable the identification of parameters critical to product quality, leading to a reduction in the number of ECs. For example, employing a performance-based approach to development can demonstrate that a material attribute that was initially considered potentially critical (in a parameter-based approach) is not actually critical and has no impact on product quality.

A decision tree (Figure 2) was modified from ICH Q12 that illustrates the stepwise approach to identifying ECs for raw material attributes and the associated submission categories (in the context of process parameters). For parameters that are not ECs, postapproval changes are not reported.

Overall, agreement with regulators on the ECs and associated submission categories can reduce the number of postapproval submissions to only the changes most critical to ensuring product quality. This provides more flexibility to implement changes and thus the ability to react more quickly to supply chain challenges. In the long term, a collaboration between regulators and industry stakeholders to develop and implement harmonized guidelines for raw materials would help address flexibility challenges, prevent delays in implementing process improvements, and ensure that both regulator and industry resources are devoted to the most critical issues.

Figure 2: Decision tree to identify ECs for raw material and associated submission categories.



CASE STUDIES

This section describes case studies of postapproval changes to raw materials and the regulatory challenges. The examples highlight the value of well-characterized raw materials and the importance of only including critical material attributes in regulatory submissions. They are representative of issues manufacturers face when attempting to address supplier and quality aspects of raw materials.

Case Study 1: Polypropylene Glycol—Removal of Noncritical Attribute from Specification

The original molecular weight (MW) specification for polypropylene glycol 2000 (PPG) of 1800–2200 was based on the Food Chemical Codex monograph (90%–110% of label) and not based on a scientific understanding of the process/product requirements. By employing an attribute-focused approach, an assessment of MW was performed based on a review of literature, process understanding, process performance, and historical PPG release testing data. The analysis showed no correlation between antifoam performance and MW, and a wider MW range of 1200–3000 was deemed acceptable for use in the processes. Based on the process performance and robustness of the raw material supply quality, it was concluded that the MW attribute is not critical and can be removed from the PPG specification to reduce the business risk without impacting the quality of the DS.

Table 2: Polypropylene glycol 2000 material target attribute profile.

Description	Polypropylene glycol, average molecular weight of 2000 Daltons	
Intended function	Defoamer	
Required characteristics to perform the intended function	• Present in sufficient quantity to achieve target concentration in process and enable defoaming. • Form droplets of appropriate size to disrupt foam under normal process conditions.	
Material attribute	**Target ranges**	**Justification/control strategy**
Appearance	Colorless to almost colorless liquid	Basic GMP requirement tested for each batch–confirms correct material received and may be indicative of impurities present.
Identification	Pass/conforms	Basic GMP requirement. Raman, infrared, or near-infrared tested for each batch–confirms correct material received and may be indicative of impurities present.
Average molecular weight	1200–3000	No correlation between PPG MW and process performance or product quality. Historical quality control (QC) data was 1875–2509 and does not trend close to upper or lower range of 1200–3000, demonstrating robustness of supply and that supplier controls ensure MW inside acceptable range.
Density	0.985–1.014	No impact
Refractive index	1.450–1.452	No impact
Water	≤ 0.1%	No impact
Viscosity	400–500 MPAS (20°C, neat)	No impact
Acid value	0.00–0.08 mg KOH/g	No impact
Hydroxyl value	40–60 mg KOH/g	Supplier release specification includes hydroxyl value which correlates to the average MW (average MW 1200–3000 corresponds to hydroxyl value 37.4–93.5). Historical hydroxyl value from manufacturer have ranged from 53.5 to 56.4 (the supplier acceptable range 40–60).

Table 3: Betaine material target attribute profile.

Description	Betaine	
Intended function	Protects cells from high medium osmolarities by providing binding sites for both positively and negatively charged species (thereby reducing osmolarity). Reduces the fraction of high-mannose oligosaccharide species.	
Required characteristics to perform the intended function	Be present in sufficient quantity to achieve target concentration in process.	
Material attribute	**Target ranges**	**Justification/control strategy**
Appearance	White to off-white powder	Basic GMP requirement tested for each batch–confirms correct material received and may be indicative of impurities present.
Identification	Pass/conforms	Basic GMP requirement. Raman or infrared tested for each batch–confirms correct material received and may be indicative of impurities present.
Water	≤ 3%	No impact to process or product: • Stability–No degradation is expected in the presence of water. • Process or product quality–Introduction of ≤ 3% water from betaine is expected to have no impact and would be insignificant in the aqueous media. • The quantity of betaine in the process–Increased water content would reduce the amount of betaine but not significantly. • The bioburden or endotoxin risk profile–Betaine solution is prepared in a Grade 8 temperature-controlled room under controlled conditions, and is filtered using sterilizing grade filters. Implementation of sampling and handling appropriate for hygroscopic materials.
Assay	≥ 98% (anhydrous basis, titration with $HClO_4$)	No impact

At the time of assessment, removal of the MW specification could be reported without requiring approval in the US and Canada and required prior approval in four regions: Australia (3 months for approval), EU (up to 6 months for approval), China (up to 10 months for approval), and Israel (required EU approval first, up to 1 year for approval). The same rationale for the change was submitted globally.

Case Study 2: Betaine—Widening of Raw Material Specification Criterion

Betaine has no compendial monograph, and the original specification included water with an acceptance criterion of ≤ 2.0%. It is a hygroscopic material that transitions to the monohydrate form on absorption of water. This results in water uptake during standard material handling and a risk of failing incoming quality control testing for the water content attribute.

A technical assessment was performed, demonstrating that increased water content is not expected to have any impact on process or product quality. Based on the chemical properties of betaine and its functional use in the process, a specification of ≤ 3% for water content was considered appropriate. In addition to specification changes, several mitigations were put in place regarding material handling.

At the time of assessment, widening of the water specification was reportable as a notification in Australia, China, and Canada. For many markets, this change did not require reporting to the health authority. This is an example of a change involving a well-characterized raw material resulting in shorter timelines to implementation.

Case Study 3: Sodium Deoxycholate—Removal of Noncritical Attribute from Specification

Sodium deoxycholate is a noncompendial white crystalline powder manufactured by neutralizing deoxycholic acid with sodium hydroxide (NaOH). The amount of NaOH added during the raw material manufacturing determines the conversion to the more soluble sodium salt and the pH in solution. The pH specification for a 10% solution was set at 8.2–10.0 to avoid precipitation at values below 8.2 caused by residual deoxycholic acid.

It was recognized that this specification for pH was not aligned with the raw material supplier specification of 7.0–9.5. Historically, the pH (average of 8.4) comfortably met the supplier specification but was close to the in-house specification 8.2–10.0. This was a supply risk due to the high probability of failing pH testing upon receipt.

A technical evaluation was performed to evaluate the impact of the pH attribute on the process performance and product quality. Because a titration step was added to the preparation of the sodium deoxycholate solution during DS manufacturing, it was recommended to remove pH from the sodium deoxycholate specification. This change improves the robustness of sodium deoxycholate supply with no impact on the DS manufacturing process or product quality.

At the time of assessment, removal of the pH specification required prior approval in Australia and New Zealand; was reportable with no restrictions in the US, Canada, EU, Great Britain, and Switzerland; and was not reportable in the rest of the world.

Case Study 4: Urea—Change from Noncompendial Pellets to USP Powder

Urea is typically the main component in the oxidation buffer in a DS process. The supplier discontinued urea in pellet form, which required a


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Table 4: Material target attribute profile.

Description	Sodium deoxycholate	
Intended function	A mild detergent in a DS manufacturing process to remove host cell impurities such as lipids, nucleic acids, contaminating proteins, and pyrogens.	
Required characteristics to perform the intended function	Be present and soluble in insufficient quantity to achieve function. Sodium salt is highly soluble compared to free acid.	
Material attribute	Target ranges	Justification/control strategy
Appearance	White crystalline powder	Basic GMP requirement tested for each batch–confirms correct material received and may be indicative of impurities present.
Identification	Pass/conforms	Basic GMP requirement. Raman or infrared tested for each batch–confirms correct material received and may be indicative of impurities present.
Loss on drying	≤ 5.0%	No impact
Assay	≥ 99.0%	No impact
pH of solution		No impact–the pH determines solubility of material. A pH control was implemented as part of the DS manufacturing process instead of at raw material release. A titration step with sodium hydroxide during the 10% solution preparation ensures the target pH is achieved regardless of the raw material pH ensuring no precipitation prior to manufacturing. The 10% solution is prepared and released as an in-process control based on a pH specification of 8.2 to 10.0.

transition to USP compendial-grade powder (from the same supplier). This resulted in a raw material specification change in which all of the specifications for the pellets were included for the powder with the same limits (except appearance) and additional tests were added to comply with the USP monograph. Buffer preparation using urea powder was evaluated, and it was determined there was no impact on dissolution, pH, or conductivity parameters. However, because the pellet form was filed with the appearance of "small colorless or white pellets," the change to powder required submission and approval of a variation by several health authorities before it could be implemented. Prior approval was required in EU, Great Britain, Australia, Switzerland, Turkey, and Israel, whereas notifications were submitted to the US, Canada, Brazil, Gulf Coast Cooperative, Egypt, and Colombia. The remaining countries considered the change as not reportable. The wide range in filing categories worldwide delayed global approval and implementation to manufacturing, which in a worst-case scenario could cause restrictions on supply.

In summary, if raw material attributes are not critical, they should not be included in the specification, because changing or removing filed specifications can take months to years, making supply more challenging to manage. Also, attributes that have high variability have an increased risk of testing failures and risk to supply. Because not all attributes with high variability are deemed critical, a risk-based approach to testing should be taken to avoid risk to supply. Therefore, it is important to identify the critical attributes early during development and mitigate any risks upfront. Defining the raw material target attribute profile could enable the identification of ECs and submission categories when using ICH Q12 principles. For example, in the case of sodium deoxycholate, the pH of the solution may have been considered an EC because it is critical to ensure material solubility and the ability to perform its function. However, through the control of pH in the DS manufacturing process, the sodium deoxycholate pH attribute is not actually critical and was determined to have no impact on product quality.

CONCLUSION

As mentioned, it is critical to have a reliable supply of raw material to maintain robust drug supply in order to serve patients. Because of shortage-related challenges, implementing a global regulatory infrastructure is increasingly needed, specifically an infrastructure that is both flexible and predictable to provide more agility to react efficiently without product delays. Leveraging ICH Q12 principles such as ECs can streamline the number of postapproval submissions. In the future, more innovative regulatory approaches, as well as supply chain approaches to manage raw materials, could be envisioned. The use of structured content and data management in CMC regulatory submissions could potentially provide a direct link to proactively manage risks in the supply chain and communicate with regulators [11].

In addition, employing the idea of quality management maturity to evaluate raw material manufacturing sites could perhaps enable an FDA rating system based on supplier excellence [12]. Ideally, a sponsor could gain some regulatory flexibility if they were to switch suppliers to one that had an "excellent" rating. Finally, through convergence and reliance, a collaboration between regulators and industry stakeholders to develop and implement harmonized guidelines for raw materials could address multiple reviews of the same material and ensure that both regulator and industry resources are dedicated to only the most critical issues, ensuring uninterrupted supply of medicines to patients worldwide.

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About the authors

Jacqueline E. Milne, PhD, is a Senior Principal Scientist at Amgen. In this role, she leads the media, chemical, and excipients technical team that provides technical expertise for raw materials in support of biologic and synthetic pipeline and portfolio programs. Prior to this, Jacqueline led the drug substance teams for numerous synthetic clinical candidates. She holds a PhD from the University of Leeds and completed a postdoctoral fellowship at MIT prior to joining Amgen.

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Jill Beierle, MS, is a Manager in Regulatory Affairs-CMC at Amgen, Inc., and is on the advocacy and external engagement team. Jill has a wide range of experience, ranging from early discovery proteomics, formulation, and quality to leading regulatory filings in early- and late-stage programs. Areas of high interest for Jill include many years of experience collaborating in cross-functional areas to identify new technologies to acquire information concerning scientific developments that can impact product development in design and data analysis for improved regulatory outcomes. A major emphasis for Jill is to be active in scientific exchange with the use of quality-driven data and scientific rationale to benefit patients in a harmonized and quality-driven, expedited approach. Jill is active in organizations such as IQ. She holds a master's degree in regulatory science from the University of Southern California School of Pharmacy. Jill has been a member of ISPE since 2021.

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William Garden has been with Amgen, Inc., for more than 25 years in a variety of roles in QA/QC, validation, and compliance. For the last 13 years, he has worked in regulatory affairs-CMC, where he is currently Director of Regulatory CMC, managing postapproval variations and life-cycle management for about 10 commercial products.

Susan E. Burke, PhD, is a Director in process development at Amgen, Inc. She leads a team in attribute sciences responsible for providing technical expertise for the materials and technologies used to manufacture Amgen's pipeline and portfolio of biologic and small molecule therapies. She oversees technical risk management, attribute data analytics, and the development of control strategy elements. Before joining Amgen, Susan led a team in Bioprocess R&D at GE Healthcare dedicated to the development of biopharmaceutical manufacturing technologies. Prior to that, Susan held leadership positions at both Allergan and Bausch & Lomb, where she oversaw formulations and process development teams. She has worked on the development of 12 commercialized products. Susan is the author of 28 scientific publications and is an inventor on 32 intellectual property filings. She has a BSc in chemistry from St Francis Xavier University and PhD in chemistry from McGill University.

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COMMUNITIES OF PRACTICE PROFILES:
Meet the Sterile Products Processing CoP

By Marcy Sanford

The members of the Sterile Products Processing (SPP) Community of Practice (CoP) Steering Committee are as diverse and varied as the topics they discuss. The CoP is comprised of professionals from around the world who are manufacturers, vendors, and consultants but all have one thing in common: the desire to improve the quality of, and reduce the risk to, the supply of sterile pharmaceutical products.

Matthew Gorton, CoP Chair and Director of Business Development at GBA, explained why this is such an important mission. "Sterile products are often introduced to a patient via injection or an infusion, which bypasses the body's normal barriers to infection: the skin and the gut system. Both are designed to keep the body safe from infection," Gorton said. "Since products that are considered sterile are introduced in ways to bypass those systems, if they are not produced or stored properly or administered correctly, they can pose a heightened risk to patient safety. The engineering controls, technologies, and regulation that our group discusses are important to ensure that the industry is increasing the quality of medicine that is consumed."

VARIED TOPICS

Because sterile products processing touches so many areas of the pharmaceutical industry, discussions at events and meetings within the CoP cover a wide variety of topics but are often focused on advanced aseptic processing and trends in aseptic filling, barrier systems, blow-fill-seal, terminal sterilization, and facility and manufacturing process design. The CoP also explores areas such as how to solve drug shortages with engineering and regulatory solutions, robotics in manufacturing, risk-based approaches to

Figures 1 and 2: Attendees and a presenter at the 2022 ISPE Aseptic Conference, which the SPP CoP participates in developing.

quality systems, barrier systems, single-use solutions, environmental monitoring, and the impacts of Annex 1. More recently, the CoP has expanded discussions to include topics around compounding pharmacies and advanced treatments like cell and gene therapy and combination devices.

"It is usually the small things that we learn during our exchanges that can tremendously help others so you're not reinventing the wheel but you're building on what others have already tried," said SPP CoP Steering Committee member Jörg Zimmermann, Vice President, Vetter Development Service, External Affairs, at Vetter Pharma-Fertigung GmbH & Co., and the 2021–2022 Chair of the ISPE International Board of Directors. "As an example, we were discussing how to use helium instead of nitrogen for overlaying in aseptic processing. My company had experience doing that and I was able to help others in the group by sharing our experience."

CONFERENCE PARTICIPATION

Gorton said CoP members are very active at ISPE conferences and training courses. They have been members of the teams producing guidance documents including the ISPE *Baseline Guide: Sterile Product Manufacturing Facilities (Third Edition)*.

Three members of the Steering Committee—Chris Schwartz, Senior Consultant, L.E.K Consulting; Jason Collins, Director of Process Architecture, IPS-Integrated Project Services; and Christa Myers, Senior Associate, Aseptic and Sterile Products Market Director, CRB—are presenting an interactive session at the 2022 ISPE Annual Meeting & Expo in Orlando. The session is entitled "Investing in Legacy Facilities: How to Get the Most Bang for Your Buck," and it will help participants learn how to assess different options for upgrading a legacy sterile manufacturing facility (e.g., transfer to alternative asset, retrofit in place, build adjacent, or build greenfield), and determine how to get the most "bang for your buck" given fixed capital allocations. The presentation will discuss decision points and implications of each option and will include an evaluation of the options against a business case framework to make a robust recommendation to leadership.

Gorton said that events like the ISPE Annual Meeting are a great place to connect with members of the Steering Committee and learn more about getting involved. Collins pointed out that his favorite part about ISPE conferences is that they give him a glimpse of the future. "Every year, technology changes and things get more interesting and by participating in activities, especially the face-to-face meetings and events, you get to see some of that equipment, sometimes on the floor, but often through presentations from vendors as they try to push the envelope on what we can do from an equipment standpoint. At every conference or every meeting, you get to see the coolest things in the industry and that's exciting."

SPP CoP Steering Committee members have also traditionally been involved with planning ISPE's Aseptic Conference (see Figures 1 and 2). Myers, who has been involved with both conferences for a long time, said, "The aseptic, barrier, and containment conference is the most forward-thinking and innovation-focused show that I have seen. The topics, the attendees, and the discussion groups focus on how to get from the current conditions of operations to a better future state while focusing on science behind the challenges. This group is astounding in the way they support each other to achieve highly functional aseptic operations. The level of collaboration for the betterment of the whole industry really makes it a special event."

ISPE AND SPP CoP BENEFITS

Overall, Steering Committee members said that the best part of being a member of ISPE and the SPP CoP is learning from each other. "The best thing about being a member of the CoP is being part of a community of a lot of people with a lot of expertise," said Christine Martin, PhD, Associate Director, AbbVie, Inc., another member of the Steering Committee. "Coming from research and development, I really like to discuss what our future looks like, what we have learned from events like the coronavirus pandemic, what challenges we have in the future, if we can in cooperation with the regulatory bodies develop timelines to shorten the approval process, and how we can apply any Lean principles to the industry and still ensure our high-quality standards."

"Being a part of the CoP gives me the opportunity to review, comment, and contribute on draft regulatory and guidance documents prior to formal release. This access and contribution helps me to be able to take that knowledge back to my organization, apply it, and help biopharmaceutical clients succeed," said Vince Cebular, Senior Vice President, IPS. Massimiliano Cesarini, Sales Director, Romaco SRL, agreed, "It allows me to bring back the insights, trends, and what we should do next in our field."

For those wishing to get involved with the SPP CoP, Gorton said the first step is joining the wider community at ISPE Engage where members can post questions and give advice. From there, he said all CoP members are happy to meet and discuss their work at ISPE events. "We really suggest people meet us. You're going find us at the Annual Meeting in Florida, and we're going to be at the Aseptic Conference next spring. We also have several of our team members that lead ISPE trainings in this space, and that's a great chance to learn some practical knowledge, best practices and operations, and stay on top of the regulatory environments."

About the author

Marcy Sanford is the Publications Coordinator for ISPE.

Pharmaceutical Engineering® is profiling CoPs in an ongoing series. This profile is the second in the series; the first profile of the Process Analytical Technology & Lifecycle Control Strategy (PAT-LCS) CoP was published in the July-August 2022 issue.

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ISPE EUROPE CONFERENCE HACKATHON: A Return to In-Person Hackathons

By Beatriz Sacristán

The Europe Hackathon for students and recent graduates was held 23–24 April as part of the activities during the 2022 ISPE Europe Annual Conference. This article provides an overview of the event and how it was organized.

The last face-to-face Hackathon took place in 2019 in Ireland, and the in-person 2020 Hackathon was postponed due to the pandemic. This year's event was organized by Emerging Leaders (ELs) of the ISPE Iberia Affiliate, including Marta Malo de Molina, Beatriz Sacristán, and Eliana Lorenzo. The organizing committee wants to thank everyone involved in organizing this event and for making it a great success.

ABOUT THE HACKATHON

A Hackathon usually lasts 24 hours, starting on Saturday when coaches give introductory presentations, followed by a workshop where participants are divided into teams and assigned the task to come up with a solution to a problem and make a presentation by Sunday morning. On Sunday, the judges evaluate the presentations, provide feedback to the teams, and decide the winner.

The main objective of a Hackathon is to divulge knowledge in an innovative scenario about the trending topics of the pharmaceutical sector, as well as to promote networking between ELs and senior industry experts.

HACKATHON FOCUS

The focus area of this Hackathon was Industry 4.0. Teams had to develop a digital transformation project for a company with low technological development and a fixed budget. Participants first received presentations from senior industry experts acting as coaches. The coaches and topics presented were:

- Michelangelo Canzoneri, Global Head of Digital and Data,

Figure 1: A team at work at the Hackathon.

Figure 2: A team working at a workshop station.

Healthcare, Merck: Roadmap to Digital Transformation
- Christian Wölbeling, Executive Industry Advisor at Körber and Torsten Isenberg, Vice President, Global and Regional Business Consulting, Körber Pharma Software: Manufacturing Execution System (MES) and Data Analytics (DA)
- Heike Roeder, Director, Lead Digital Quality, Risk Advisory Life Science, Deloitte: Quality Management Systems (QMS)
- Zen-Zen Yen, Head of Maintenance Operations, Bayer AG: Predictive Maintenance (PM)

After the coaches' presentations, participants were divided into four teams with a total of 16 participants. Each group was assigned a company with several details of the company such as batch size, production costs, and batch lead time. The four types of companies were:
- Generics (CMO): Tablets manufacturer
- Biotech company: CAR-T cell therapy
- Personalized medicines: Immunology (allergy vaccines)
- Medical device: Glucose meter device

Each group received a fixed budget to make their company the most attractive to the investors (judges) by establishing a business case for a digital transformation project. With their budget, each team had to go to four stations, named after places in Madrid, and work on the topics (MES, Data Analytics, QMS, and Predictive Maintenance). The challenge was supposed to take place in popular places within the beautiful city of Madrid, but due to bad weather conditions the participants had to stay inside the hotel.

At each station, the teams encountered a challenging situation related to each topic. The teams were presented with three options to solve the challenge, where each option implied a different digital solution, implementation cost, time, and other resources. One of the provided options had to be chosen before leaving a station and going to the next to promote fast and final decision-making. The teams only had 15 minutes per station and had to think wisely about how to invest their budget according to the characteristics of their company, and not spend it too fast!

After the team went through the four stations, they faced the difficult part: building the business case based on the digital solutions they chose to implement, and making their company the most attractive to the investors (the judges). Teams worked on their business cases through Saturday with the support of the coaches.

On Sunday morning, each team presented their company to the judges. The teams did outstanding work in less than 24 hours, creating companies that seemed real with names and logos, bringing the judges close to their companies. The winning team even made a short commercial!

After the presentations, the judges evaluated the presentations as potential investors, provided feedback to the teams, and chose the winning team. This team received attendance at the 2022 ISPE Pharma 4.0™ & Annex 1 Conference on 7–8 December in Vienna, Austria. Congratulations to Joshua Wise, Melanie Austrup, and Roland Wölfle, members of Feronia, the winning team!

> The main objective of a Hackathon is to divulge knowledge in an innovative scenario about the trending topics of the pharmaceutical sector, as well as to promote networking between ELs and senior industry experts.

Judges for the Hackathon were Canzoneri and Wölbeling (both also served as coaches); Ana Maqueda, Site Leader, Pfizer Global Supply; Richard Denk, Senior Consultant, Aseptic Processing and Containment, SKAN AG; and Teresa Minero, CEO and Founder, LifeBee Digitalizing Life Sciences.

AFTER THE EVENT

The Hackathon was presented by the organizers and a member of the winning team on 25 April to the full 2022 ISPE Europe Annual Conference, and received great feedback from the attendees. It was a great opportunity for the ELs to be seen and heard by senior experts in the industry.

The EL European Hackathon proved to be an outstanding event once again! The organizers want to give special thanks to the coaches and judges who helped us with the organization, and to the participants whose enthusiasm and joy made this a great event. Participants made new connections and we hope to see all of them again at the next Europe Hackathon in 2023.

About the author

Beatriz Sacristán works as Packaging Operations Manager with Pfizer at the Madrid site, where hemophilia products are manufactured, packaged, and distributed worldwide. She holds a BSc in pharmacy and has eight years of experience in the pharma industry in a variety of roles of increasing responsibility, including quality operations, quality validations, manufacturing support, and packaging operations. Beatriz has played an active role with ISPE Emerging Leaders since 2017 and is Co-chair of the ISPE Iberia Affiliate Emerging Leaders. She has been an ISPE member since 2016.

ISPE EUROPE CONFERENCE HACKATHON:

Participants Combine Technical Knowledge and Entrepreneurial Mindsets

By Robin Schiemer

Four teams of Emerging Leaders (ELs) represented one of four different company manufacturer types in the EL Hackathon at the ISPE Europe Conference. This article provides some participants' views of the event.

The theme of the Hackathon was Pharma 4.0™: Digitalization Roadmap. Using different business models and production equipment, each team worked together over the weekend to solve a problem set forth to all teams. A panel of judges determined which team produced the best strategic solution.

Based on a fact sheet provided by the organizers, the teams defined the status quo of their respective companies and then went into the first part of the challenge. Given a fictitious budget of €800,000, the teams were asked to make investment decisions in four specific areas: manufacturing execution systems, quality management systems, data analytics, and predictive maintenance. In the second part of the challenge, the teams prepared a company pitch for a group of investors (represented by the Hackathon judges) that built on their respective company profiles and investment decisions.

THE PROCESS

After an initial presentation series on the four focus topics, the teams were assembled by the organizers and went into a definition phase. The groups needed to quickly find answers to difficult questions. In the subsequent investment phase, decisions about acquiring new technology or equipment were accompanied by discussions within the teams and with the coaches who supported each team. Participant Natalie Schützler, Sanofi, described the process by saying, "We were being placed in this situation where none of the members of our group had learned about this particular topic before, but we knew we would have to make a decision

Figure 1: Participants and coaches from the ISPE D/A/CH Affiliate at the Emerging Leaders Hackathon in Madrid. From left to right: Christian Wölbeling, Melanie Austrup, Paul Heiden, Natalie Schützler, Roland Woelfle, Robin Schiemer, Fabian Bamps, Michelangelo Canzoneri, Dany Shami, and Zen-Zen Yen.

Figure 2: Natalie Schützler during her team's pitch to the judges.

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within the next 10 minutes." Despite the time constraints, she said, "we somehow managed to find a pretty neat solution."

After the investment phase, the profiling phase began. In this phase, the teams reassessed their company profiles and how their somewhat spontaneous investments could be turned into a long-term operation strategy. The goal was to prepare a convincing pitch for increased investments. However, this was not as straightforward as it may sound. The coaches, who are senior experts in the pharmaceutical industry, helped the teams with context to turn their ideas and questions into feasible solutions, working until early Sunday morning.

Team participants had to find answers to questions such as:

- What does our production process look like?
- Who are our stakeholders?
- What are our objectives and where do we need to improve?
- What are our bottlenecks?
- What is the best way to increase our productivity while keeping costs low?
- What is the long-term benefit of acquiring this technology?

If you are an Emerging Leader and looking forward to solving an exciting business case in combination with a cool networking event, you should not miss the next Hackathon!

After an intense 24 hours, including a networking dinner and drinks, all teams pitched their ideas to a panel of judges Sunday morning. The teams presented their strategies and were questioned by the judges regarding their expansion plans, financials, and technological progress.

Thanks to an almost-perfect pitch, an unerring company board, and a hilarious advertisement clip, the team of Feronia won over the judges with their biotechnological platform for allergy treatments.

OVERALL IMPRESSIONS

The Madrid Hackathon was an incredibly fun and challenging experience. I can recommend that every recent graduate or EL in the pharmaceutical industry join this exceptional event. If you like to go out of your comfort zone, discuss the challenges of tomorrow, and switch into the roles of a process engineer, management executive, and a business developer over 24 hours, this is definitely for you.

Here are some impressions from three fellow participants from the EL community.

Roland Wölfle, Head of Automation and Robotics, pester pac automation GmbH, said, "The ISPE Emerging Leaders Hackathon in Madrid was the perfect event for motivated young talents who want to find out where their limits are. The special atmosphere and creative mood among the participants, who were all highly qualified, resulted in a great experience. My personal highlight of the competition was the moment when the team felt that the ideas of the individual group members created a bigger picture and we realized that it could really work. I would call that electrifying. Nobody had to comment on this moment; we just understood and were happy."

Natalie Schützler, Change Leader, Sanofi, said, "I joined this year's Hackathon in Madrid because I wanted to take on an exciting challenge with a team of motivated young people and looking back, I can say that totally was the case. It was a great experience! Besides meeting Emerging Leaders from all over Europe, I also had many opportunities to chat with long-time ISPE members and experts from the pharmaceutical industry, which was so cool and interesting. So if you are an Emerging Leader and looking forward to solving an exciting business case in combination with a cool networking event, you should not miss the next Hackathon!"

Natalia Vtyurina, Senior Quality Assurance Officer at HALIX, said, "I joined the ISPE Hackathon , 2022 in Madrid because it was a great opportunity to network with my peers from all over Europe by working closely together with them in the teams. The topics of the ISPE Hackathons are chosen based on the latest trends in the pharmaceutical industry. This is why participation at the Hackathons provides exceptional knowledge and gives an advantage to be the first one to learn all the challenges and success stories from the experts. This year, we worked on the business cases for Industry 4.0 digitalization roadmap, an extremely important topic that will become more and more popular for implementation in the next years and decades. The highlight for me was getting introduced to my team members with different backgrounds and very quickly becoming an efficient team supporting each other in reaching our goal by solving our business case in a very squeezed time frame of less than 24 hours. You must try it and you can learn so much about yourself!"

About the author

Robin Schiemer is a PhD candidate at Karlsruhe Institute of Technology (KIT), Germany, focusing on data science applications for downstream process development (DSP). He holds a master's degree in bioprocess engineering from KIT and has gained industry experience in process modeling and process analytical technology in biopharmaceutical DSP. Robin has been a member of ISPE since 2017 and is the Co-chair of ISPE Europe Emerging Leaders.

Volunteer Week 2022: A Success

By Marcy Sanford

ISPE has more than 19,000 members from more than 129 countries, and many of them spend countless hours sharing their knowledge and connecting with others, helping ISPE to advance the educational and technical efficiency of all members.

Earlier this year, some of those volunteers were honored during ISPE Volunteer Week. Carrie McManus, ISPE Manager of Member Engagement, said Committee, Chapter, and Affiliate leadership teams were asked to nominate volunteers. "We wanted to recognize and thank the volunteers who are behind the scenes, working very hard to help ISPE accomplish its mission, but who are not usually in the spotlight."

Honorees were celebrated throughout the week with profiles on the ISPE iSpeak blog and through social media. McManus is already planning next year's Volunteer Week and plans for the program to grow each year. "Every year, we want to be able to add something extra to celebrate our volunteers. For 2023, we're hoping to include programming that will be open to all volunteers and provide members who are interested in volunteering with more resources and information on how they can get involved."

McManus said members don't have to wait until 2023 to get involved. "ISPE members have numerous ways to get involved on a local level to global level. We have volunteer opportunities available year-round, from short-term and long-term projects to being part of a committee or special interest group. If members would like to volunteer, we can find the right fit for them."

To see the 2022 ISPE Volunteer Week profiles and learn more about volunteer opportunities at ISPE, visit https://ispe.org/membership/volunteer

About the author

Marcy Sanford is the Publications Coordinator for ISPE.

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WINNER 2022 APEX AWARDS FOR PUBLICATION EXCELLENCE

Pharmaceutical Engineering® Article Receives 2022 APEX Award

Pharmaceutical Engineering has won a 2022 APEX Award for Publication Excellence in the Technical & Technology Writing category for "AI's Promise for ATMPs," published in the November-December 2021 issue.

The winning article was written by two ISPE members, William Whitford and Toni Manzano. Whitford is Life Science Strategic Solutions Leader for DPS Group. He is a leader in research and development for biomedical and biomanufacturing applications, Industry 4.0, and digitalization with over 300 articles, book chapters, and patents published.

Manzano is Co-Founder and CSO at Aizon, and has led software projects for pharmaceutical companies for over 25 years. His current company provides big data and artificial intelligence (AI) software as a service (SaaS) platforms for the biotechnology and pharmaceutical industries.

AI AND BIOPHARMA

"We have finally seen significant gains in pharmaceutical science and manufacturing operations through the application of AI," Whitford said. "That AI's power can apply to biopharmaceuticals is exemplified by AI's heralded success in providing biomolecule structure prediction through, for example, Alphabet's/Google's DeepMind AlphaFold."

"AI's specific power in ATMPs include aiding in patient-distal autologous cell sample processing issues and supporting their continually evolving practices," Manzano said. "The complexity and variability associated with the cellular process for patients, where in extreme cases, each batch would be related to a single patient, can only be adequately managed by AI mechanisms. Cytoskeletal organization, cell morphology, and other biological characteristics can only be automated using AI to deliver the right drug at the right time to patients."

Read the full article is at https://ispe.org/pharmaceutical-engineering/november-december-2021/ais-promise-atmps

PE AWARDS

This is the third year in a row that *Pharmaceutical Engineering* has been recognized with an APEX Award.

A 2021 APEX Award of Excellence was awarded to the four-article "Special Report: COVID-19 Impact" series, published in the July-August 2020 issue, in the category of COVID-19 Media–Government/Association content (https://ispe.org/pharmaceutical-engineering/july-august-2020 special-report-covid-19-impact).

A 2020 APEX Award of Excellence was given to "Blockchain for Pharmaceutical Engineers," published in the January-February 2019 issue, in the category of Technical and Technology Writing (https://ispe.org/pharmaceutical-engineering/january-february-2019/blockchain-pharmaceutical-engineers).

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—Susan Sandler, Senior Director, Editorial

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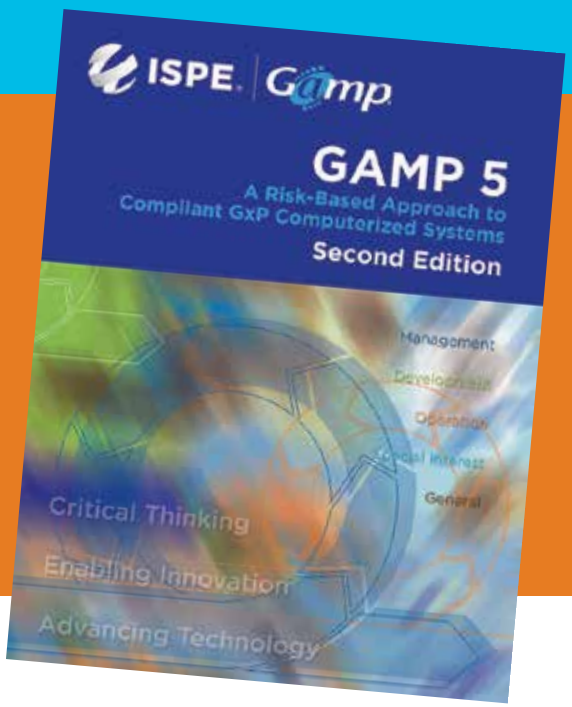

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New GPG Promotes Continuous Manufacturing of OSD

The pharmaceutical industry began applying the principles of continuous processing to the manufacture of oral solid dosage (OSD) forms in the mid-2000s. The consensus among experienced practitioners is that the continuous approach has numerous benefits.

According to Guide Co-lead Dave DiProspero, Director of Pharmaceutical Process Technology, CRB, "Continuous manufacturing provides for a full range of product life cycle, from small-volume clinical production to large-volume commercial production, with minimization or elimination of scale-up activities, all leading to real-time release. It offers potential safety benefits and requires a smaller facility footprint."

However, there are still many challenges to widespread adoption. The ISPE OSD Community of Practice formed a working team in 2017 to advance the use of continuous manufacturing in the pharmaceutical industry and to increase the long-term efficiency and affordability of the manufacture of OSD products.

The team, composed of end user pharmaceutical companies, equipment vendors, and academics, set out to establish equipment requirements, identify opportunities for harmonization and flexible integration, and suggest enhancements to current equipment. The collective output forms the basis for the ISPE *Good Practice Guide: Continuous Manufacturing of Oral Solid Dosage Forms*.

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

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

—Marcy Sanford, Publications Coordinator

Meet the ISPE STAFF

DOUG WHITTEMORE

In each issue of *Pharmaceutical Engineering*®, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Doug Whittemore, Account Manager, Sales Team.

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

I build authentic business relationships with both current and new customers. It all starts with understanding their marketing and sales goals, working in partnership to develop solutions providing the best fit and value for each customer. My goal is to create and nurture lasting, mutually successful business relationships.

What do you love about your job?

I have the pleasure of working closely with not only ISPE customers but the ISPE staff team as well. I partner with staff throughout the organization in developing corporate offerings and in communicating these offerings to interested customers. I thoroughly enjoy the camaraderie and teamwork here at ISPE; I am very fortunate to work with such a wonderful team.

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

Well, since I am a self-proclaimed workaholic, this is an interesting question. Since I live in Tampa, Florida, not far from the water, I enjoy sitting at an outside beach restaurant with a cold beverage watching both a good ball game and the beautiful beach. I also enjoy a good John Wayne movie and listening to Frank Sinatra.

VALIDATION 4.0:
Case Studies for Oral Solid Dose Manufacturing

By Brad Swarbrick and David Margetts

Three case studies on Validation 4.0 demonstrate how quality by design (QbD) principles, when applied with digitization, can verify processes in scale-up and technology transfer, and why blend and content uniformity matter for tablet integrity.

This article provides background on Validation 4.0 and presents case studies on applying Validation 4.0 in oral solid dose (OSD) manufacture. The ISPE Validation 4.0 Special Interest Group (SIG), part of ISPE's Pharma 4.0™ initiative, has written on the issue of Validation 4.0 previously in this magazine, first in "The History & Future of Validation" to provide history and overview of validation in the pharmaceutical industry and a definition of continued process verification and continuous process verification [1]. The group also published "Laying the Foundation for Validation 4.0" [2], discussing how the topic of validation has been "a central obstacle to adopting new concepts for quality," and has indirectly slowed the uptake of the very technologies that are required to bring pharmaceutical manufacturing into Industry 4.0.

HISTORY OF QUALITY BY DESIGN

OSD manufacture is a multifaceted operation consisting of raw materials and unit operations that transform the raw materials into finished product. Traditional approaches to process development and validation involve the manufacture of validation batches to show that the combined unit operations and raw materials produce intermediates and finished products that meet a predefined set of efficacy and performance characteristics.

Major issues in the traditional approach to validation are the lack of information on representative sampling; the difficulty of real-time monitoring and control; and the snapshot, rather than continuous manner, in which validation is performed.

In 2011, the US FDA released an updated process validation guidance document [3] and included the concept of "continued process verification" with routine monitoring of process parameters and trending of data to have a process that is capable of consistently delivering quality product. They referred to ASTM E2500-07 [4], which states that quality by design (QbD) concepts should be applied to ensure that critical aspects are designed into systems during the specification and design process. In this article, there is no distinction between the terms "continued process verification" and "continuous process verification" with regard to US and EU definitions.

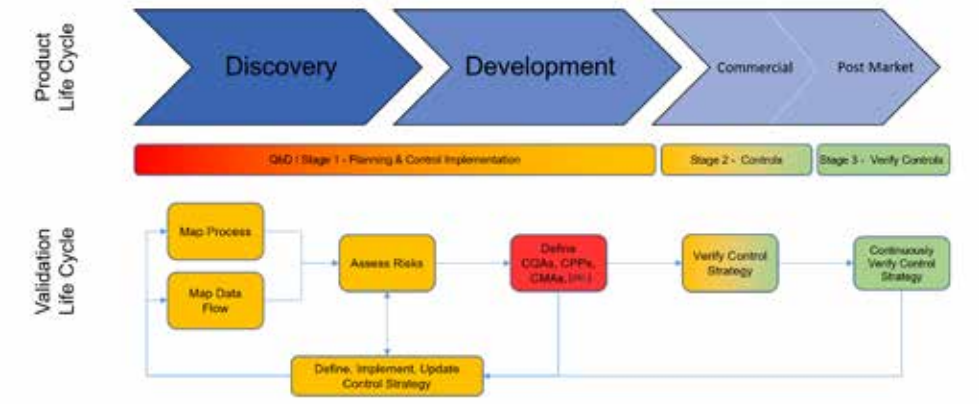
Industry 4.0 as an Enabler of QbD

To verify the consistency of every batch in a sufficiently timely and accurate fashion, and to cope with inherent variabilities, some level of digitization is required. Information technology is not mandatory for QbD; however, the case studies show the capabilities of modern data systems for effective process understanding and control. Those that are increasingly available and accessible can improve product quality and efficiency and produce better medicines at lower manufacturing cost.

Industry 4.0, as a global manufacturing revolution, relies on collecting and using data in electronic formats to understand and improve process and product performance beyond legacy paper and manual methods [5]. QbD has a similar philosophy and encourages manufacturers to start their validation efforts at product conception so that control strategies are built into the process, by design. This also ensures that when the process is moved, or scaled up to commercial manufacturing, the entire quality strategy is in place. Increasingly, the pharmaceutical industry is looking to digitalization as an enabler of QbD using data from all available sources. The following case studies and the capabilities described in this article are simply not practical without modern measurement sensors and data analysis tools.

In 2004, the US FDA published its process analytical technology (PAT) framework guidance to promote the use of innovative technologies for the collection of timely quality data that ensure the quality of product throughout the entire manufacturing process, from raw material dispensing to packaging [6]. Together a combined QbD/PAT approach provides a solid platform for continuous verification and digitalization, particularly when linked to digital solutions and ways of working such as manufacturing execution systems (MES), supervisory control and data acquisition (SCADA) systems, and industrial databases that allow fast

Figure 1: Stage 3 of the Validation 4.0 model focuses on continuous verification as a targeted result of QbD.



retrieval of data over multiple batches, months, raw materials, and lots. This knowledge management within systems can be used to optimize manufacturing and allow some flexibility within design constraints.

It has been 20 years since the FDA released "Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach: Final Report" [7], and during that time, improvements in computing, data warehousing, sensor technology, and control systems now provide OSD manufacturers with the digital tools to address the validation requirements associated with continuous verification/validation and to move to Industry 4.0/Pharma 4.0™ and Validation 4.0 with confidence.

Validation 4.0 Is QbD-Centric

This article is focused on Stage 3 of the Validation 4.0 model (as shown in Figure 1). Verifying controls is done continuously with a frequency dependent on the ability to measure and identify risks from a process and systems perspective. One of the goals of Validation 4.0 is that Stage 2 ultimately absolves by moving directly to a state of continuous verification.

Traditional OSD manufacturing consists of a series of disjointed unit operations that transform raw materials and intermediates into finished products. Such processes are batch processes and transform large, bulk powders via the unit operations. OSD manufacture typically has a number of processes to deal with different raw material properties such as direct compression, roller compaction, and high shear granulation.

No matter which approach is taken, there is a common variable that is commonly overlooked in all three processes: raw materials. Raw materials are typically assessed using pharmacopeia monographs that focus on identification and purity aspects alone. The samples assessed are typically nonrepresentative and do not provide any information on how the materials will perform in the process.

QbD allows a manufacturer to build flexibility into manufacturing processes, rather than keeping the process fixed. If the process is fixed, inherent raw material variability cannot be accommodated by the process. This leads to substandard intermediates that, more often than not, result in issues in compression. Through improved sampling techniques and measurements from the initial stages of manufacturing, better understanding of the raw material variability allows the development of conformity or classification models. And technologies such as near-infrared (NIR) spectroscopy and powder characterization are used to understand the "process-ability" of materials.

In the QbD and Validation 4.0 world, digitalization tools and systems can use this information to adjust the process. Thus, QbD needs to assess all sources of variability, including inputs from outside the manufacturing floor, because variability from suppliers' products can impact regulated customer's processes. The ability to adjust a process is not unlimited and must be bound by certain rules that ensure quality. In QbD terminology, the boundaries around the process are known as the design space. By definition, the design space is established by design, i.e., through timely measurements that are linked to quality, or that are defined as critical quality attributes. The QbD approach has also introduced a new vocabulary associated with modern manufacture. Some of the important terms include the following:

- Quality target product profile (QTPP): Efficacy and performance characteristics that ensure the safety of the end user. Essentially, this defines the target product.
- Critical quality attributes (CQAs): Attributes of the product that ensure it is fit for its intended use when assessed against the QTPP. Essentially, these define the attributes that need to be met to meet the target product.
- Critical process parameters (CPPs): Controllable aspects of the manufacturing process that ensure the CQAs meet their defined targets. Essentially, these define what needs to be controlled so that the attributes will be met.
- Critical material attributes (CMAs): Attributes of the input materials that should be within appropriate limits or distribution to ensure the desired quality of the product.

Based on the previous points, validation becomes product- and

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QbD allows a manufacturer to build flexibility into manufacturing processes, rather than keeping the process fixed.

process-centric through measurement data to maintain manufacturing within the design space, the resulting allowable limits of all the critical attributes and parameters that result in product that meets the QTPP requirements (also known as the desired state).

When a formulation is robust and the raw material characteristics are understood, the process can be adjusted within the design space, resulting in the highest-quality finished product. To fully achieve this and to incorporate it into an industrial production line, digitalization tools and appropriate sensor technology are required.

AN INTRODUCTION TO CONTINUOUS VERIFICATION

A recent trend in pharmaceutical manufacturing is to move to continuous manufacturing (CM) systems. A CM system is a connected series of unit operations that converts small amounts of raw materials and intermediates at a time in small-scale equipment with much higher control and better sampling opportunities. The small amounts of materials processed at a time are called sub- or micro-batches. The combination of many sub-batches makes up a final batch, which is packed off while the next major batch starts and continues until the process is stopped.

In continuous manufacture, there is reduced opportunity to take physical samples from the process and assess them offline. When samples are removed, traceability becomes a problem, so timely information is required through highly digitized processing equipment and sensor technologies. In a CM system, every sub-batch is monitored and assessed for quality, thus providing a process chronology traceable back to unit doses in some cases. Such systems are not possible without QbD principles, PAT, and digitalization. In these types of systems, a real-time release strategy can be built into the process by design, allowing for materials to pass continuously through all unit operations to packaging and release without laboratory testing.

The principles of CM can also be applied to batch manufacturing operations if due consideration is given to better understanding of raw materials and correct process sampling strategies, based on large N sampling plans. To make large N sampling effective from an economical sense, the nondestructive, inline analysis of CQAs by PAT is required. In many cases, these PAT sensors will be NIR sensors and the data and models have to be taught by generating many spectra of the desired material. So there is a longer development phase when using PAT as a tradeoff to an improved process understanding and higher efficiency commercial production phase.

QbD and Continuous Verification

The basis for implementing QbD is described through the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidance documents Q8, Q9, and Q10 [8]; how they relate to ASTM [4]; and the US FDA's guidance and GMP priciples [3, 6, 7].

ICH Q8 establishes what is relevant for product development based on QbD principles and defines the concept of design space [9]. The establishment of design space results from consideration of the risks to quality (ICH Q9), and the methodology used in these case studies starts with design of experiments and multivariate data analysis (MVDA) approaches to build predictive models based on available digital information from process equipment and process sensors. The iterative nature between Q8 and Q9 allows risk mitigation and the knowledge obtained is managed by the pharmaceutical quality system (PQS) of ICH Q10 [10].

Extending the concept of the PQS in Validation 4.0 is knowledge management as a repository, where digitized information collected from real-time measurements is used in conjunction with process models. These models were developed during the early-stage development learning/design phases, which ensure the process is operating within the design space and thus producing product in its desired state.

Data systems for QbD aspects of Validation 4.0 include:

- Electronic process definition and control (i.e., integrated manufacturing execution system / electronic batch records for manual operations with underlying industrial internet of things [IIoT], supervisory control and data acquisition systems, or distributed control systems for running automated equipment)
- Industrial databases that collect real-time data, alarms, and events (i.e., data historian)
- PAT knowledge management systems (a useful explanation of PAT systems is provided in *Multivariate Analysis in the Pharmaceutical Industry* [11]).

These systems operate synchronously and are used to detect and correct issues before they become problems and deviations. This is in contrast to the traditional manufacturing process, where correction is usually impossible and rework/quarantine and scrap is usually the result.

Process controls and digitized process equipment, combined with process sensors, assess the health of both the process and the product, as it exists in the process without unnecessary physical sampling. It is important to note that such systems are not about bringing the laboratory to the process, but rather about using the information to detect slight changes in materials and provide flexibility in the process operation. If only quantitative testing is the goal, this is quality by testing (QbT) and defeats the purpose of implementing technology to manage real-time control and assurance of QbD. Quantitative assessments of potency are to be considered side benefits of the QbD approach, not the major driver.

Figure 2 shows how digitized recipe systems, once integrated to process sensors and data that represents the process signature,

allow a complete and continuous assessment of the entire batch, effectively making every batch a validation batch.

CASE STUDIES FROM OSD MANUFACTURE

The case studies outlined in this article are from oral solid dosage-type production; however, the principles are applicable generally and the objective of this article is to encourage similar approaches and applications across the Pharma and Biopharma industry. The following case studies are from different types of OSD manufacture and are representative for both batch and CM systems. A typical OSD process starts with raw materials, dispensing of raw materials, milling/sieving, blending, compression, coating, and packaging. The operations of granulation (wet or dry) differ with the raw material and are a particle engineering step used to provide the granule properties conducive to uniform blending. Powder blending is one of the least understood of scientific processes and is influenced by many aspects of materials, including their size, shape, density, electrostatic nature, and moisture content. Without a complete understanding of raw material characteristics, process improvement and optimization are very difficult.

Many organizations globally are starting to adopt PAT systems for a number of unit operations, particularly focusing on blend uniformity. When these companies monitor blend uniformity using technologies such as NIR spectroscopy, they are often disappointed with the results obtained. When a process is measured at the microscopic level, the flaws associated with traditional validation approaches are revealed. This may sound surprising and, in many cases, a manufacturer will argue that their product has been manufactured without variability issues for years. A quick review of batch documents, however, tends to reveal a long list of process deviations and reworks, simply because current validation strategies are short term, rather than long term and performance focused.

Case Study 1

The first case study shows why the blending stage is typically the wrong place to start with PAT for process improvement, because operations have already transformed raw materials into intermediates before blending is performed.

Some raw material suppliers provide active pharmaceutical ingredients (API) that are pre-granulated so that the secondary manufacturer can produce tablets using direct compression batch manufacturing process. During the validation stage of the process, a traditional three-batch approach was used, whereas typically the raw material supplier sends exhibition batches of their material and the manufacturer typically assigns the company's best operators and analytical staff to perform the validation. In this scenario, the validation is already biased.

Problems start to arise soon after process validation is approved, and in one situation, the quality control (QC) laboratory allowed the material to pass based on pharmacopeia identification and purity testing. Process operators noted that the new raw

Figure 2: The relationship between digitized systems enabling Validation 4.0 continuous verification.

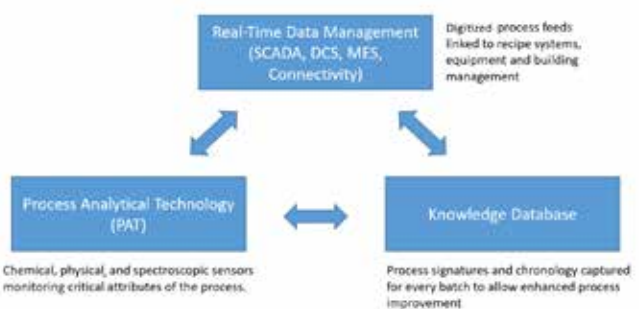
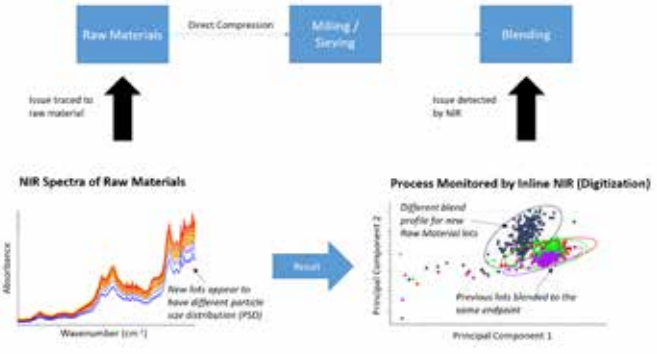


Figure 3: Process investigation to establish the root cause of a major issue in blend uniformity and compression.



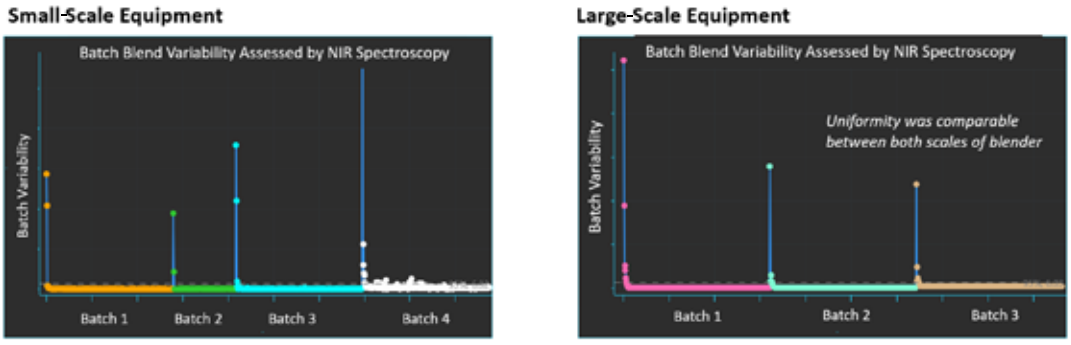
material lots were free-flowing at the top of the bags, but as they started to empty the bottom, heavier screening was required. The company decided to invest in NIR spectroscopy to evaluate the process and to cope with the expected high throughputs of the new product introduction.

The first observation was that the NIR detected a distinct difference in the original raw material lots and the new lots, even though they passed pharmacopeia testing. Figure 3 summarizes the findings of an extensive process investigation.

Using a combined NIR spectroscopic/chemometrics approach, deviations from the expected process signature were observed. When these issues were traced back to the raw materials, it was found that the particle size distribution (PSD) of the new lots was inconsistent. NIR spectroscopy is capable of detecting median particle size changes and this inconsistency resulted in more fines, based on lots that were not blended properly that had uniformity and compression issues.

As stated previously, granulation is the process of engineering particles to tight PSDs so that they are matched to the other material, allowing uniformity in blending. This is not homogeneity because a homogeneous material is perfectly mixed and is an impossible state in reality. Better terminology is heterogeneity minimization, which is more appropriate for pharmaceutical

Figure 4: Process scale-up between two commercial-scale blenders using a QbD/PAT approach.



blending operations. This example highlights the need to understand the raw material as the first stage of OSD manufacturing process validation and shows how technology can measure changes in raw materials and the characteristics of intermediates. Technologies such as NIR spectroscopy, inline particle sizers, and other sensors working in combination can be used to develop process models that assess data in real time and allow feed-forward process control.

Case Study 2

A second case study focuses on the scale-up of a blending process from one commercial manufacturing batch size to a large batch size. The intermediate bulk container (IBC) geometry is similar between the two blenders, with one offset at 15 degrees and the other at 30 degrees off axis. Because the smaller scale process is considered validated, it can serve as a baseline when comparing the results to the larger blender.

Inline NIR spectroscopy was used for the evaluation and the results are summarized in Figure 4. The blend is a high-dose API formulation and can be monitored for uniformity using inline NIR spectroscopy. A spectrum is collected after each rotation of the blender and as the heterogeneity minimizes, spectra collected will begin to look consistent with each other. Statistical methods can then be applied to the data, resulting in the blend curves shown in the figure. In all cases, the endpoint was established rapidly compared to the endpoint established by traditional validation approaches.

The results in Figure 4 highlight the principles of Validation 4.0 continuous verification and why digitalization is such an important enabling tool for QbD. However, this does not negate the need for the application of suitable processing engineering mechanisms. In the preceding example, blend uniformity can be established without physically sampling the powder bed, whereas the traditional validation approach used sample thieves to extract nonrepresentative specimens from spatial locations. Not only is it impossible to representatively sample a three-dimensional lot, but the sampling errors induced by using a sampling thief contained 10 to 50 times the errors in the analytical instrumentation used to determine potency. We found that the traditional validation approach required 10 to 20 times longer blending of the product, which can induce demixing and reduction in particle size of softer materials.

This is one of the main reasons the US FDA has questioned USP <905> (Uniformity of Dosage Units) [13] as a method for establishing blend and content uniformity. The shearing and electrostatic forces induced by physical sampling devices can destroy blend uniformity and provide false information on true blend endpoints. The NIR spectra provide digital information in real time of the state of powder mixing and the process can be stopped when the desired state has been reached. This is an outcome of the philosophy of PAT that must be translated to Validation 4.0, i.e., processes are ready when they are ready. Fixed-time processing is not in alignment with QbD or Validation 4.0 and technology must be used to continuously verify when the desired state has been achieved.

In one example, a manufacturer wanted to validate the NIR method against physical aliquots extracted from the blender using a spatial sampling plan. After extraction of the aliquots, the blender was restarted and the NIR spectrometer indicated that the entire uniformity of the blend was lost. Uniformity was reestablished after 60 further rotations and the original blended state was not reached. Again, digitalization and no physical sampling were able to establish the correct endpoint of the process and using PAT, a continuous verification strategy was established.

Case Study 3

In tablet compression, each tablet produced is a 100% statistically representative sample. The sample delivery of powder to the feed frame of a compression machine resembles the most accurate sampling device currently available: A spinning riffler. A rotary compression machine can be visualized as a compacting spinning riffler and therefore analysis of single tablets is a true representation of blend and content uniformity.

Because blending does not stop until compression, an opportunity exists for manufacturers to monitor uniformity in real time at the feed frame of a tablet press. In this case study, a NIR spectrometer is located on the spider wheel and is used to ensure representative sampling, and the NIR spectrometer can measure

Figure 5: Control chart of a tablet compression run monitored by NIR spectroscopy.

content uniformity in real time and report the data in control charts. When only random variations around a target value are observed, this can be used to establish that the blend has retained its integrity during transfer and that the content uniformity is confirmed.

The 100% measurement of individual tablets is practically not possible; however, due to the representative nature of the sample in the feed frame, pseudo 100% verification of blend and content uniformity is established. This is an example of the true nature of the scientific, risk-based approach outlined in "Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach: Final Report" [7].

The European Medicines Agency has published a "Use of Near Infrared Spectroscopy (NIRS) by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations" [12], which allows PAT applications to produce trend data for quantitative

analyses. In this example, the NIR results represent uniformity of blend, then by measuring at the feed frame, content uniformity can be established through consistency in control charting.

The first step of monitoring at the feed frame uses digitalization to establish uniformity. The second step is a traditional approach where tablets are collected at uniform time periods over the compression run and assayed using the reference laboratory method. Because the samples obtained are representative, the first validation batch can be comparative and subsequent validation and continuous verification batches can all be monitored by inline PAT methods. Figure 5 shows the results obtained from two IBC bins run on a compression machine and assessed by inline PAT. The Y-axis can be a predicted value using a validated chemometrics model or a specific and selective wavelength that corresponds to changes in API or other important components. As is typical, during changeover of IBC blenders and tablet press startup, deviations can be observed in the control charts. Such tablets can be rejected off the line until uniformity is established and then tablets can be collected for coating or packaging.

CONCLUSION

The world is rapidly becoming fully digitized, and concepts like the IIoT and Industry 4.0 have led to innovations in rapid data storage and use. Validation 4.0 must leverage these concepts and fit them into established QbD and PAT initiatives currently being adopted by the pharmaceutical industry and related industries.

New PAT instrumentation with smaller footprints and higher sensitivity are constantly being developed; when used correctly, they can allow manufacturers to become innovative and reduce or eliminate the need for physical sampling and offline analysis. This allows industries to apply the principles of Validation 4.0 to control and assure the quality in real time for every batch with an applied knowledge and data-driven intelligence from historical trends. Thus, Validation 4.0 is maintaining a chronological history through data of the entire manufacturing process and when deviations are detected, these finding can be analyzed by methods, either statistical or chemometrics, to establish the root causes of the issues and develop control strategies to minimize the occurrence of such events in the future.

The key takeaway is that the principles of Validation 4.0 are proactive, not reactive. Under the old paradigm, traditional approaches were biased and based on selecting batches with the best raw material, operators, and analysts as a baseline to pass product for release. In Validation 4.0 and a truly QbD system, the use of data models, PAT, and feed-forward/feedback control establishes a process chronology and digital signature for comparison to past and future batches. Therefore, digitization and QbD allows for true validation of every batch.

Please reach out to the Validation 4.0 SIG with your questions and to share your views, thoughts, case studies, and concepts on new methods that will better assure quality in pharmaceutical and biotechnology manufacturing. The Validation 4.0 community welcomes your input.

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Brad Swarbrick is the Owner of Quality by Design Consultancy, specializing in the implementation of PAT solutions into the pharmaceutical and related industries. Brad is also a Co-founder of KAX Group, specializing in multivariate data analysis software solutions. With over 20 years of experience in the application of PAT and chemometrics, including being part of the Pfizer global PAT group, Brad has implemented many systems into pharmaceutical manufacturing operations globally. Brad has a PhD in biospectroscopy from the University of Sydney and is the current pharmaceutical section editor of the *Journal of Near Infrared Spectroscopy*. Brad is also the author and co-author of a number of textbooks and articles on PAT and chemometrics, including co-authoring the *Multivariate Data Analysis in Practice* textbook.

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NOVEL DRY DECONTAMINATION METHOD USING

Gaseous Chlorine Dioxide

By Mark A. Czarneski

Chlorine dioxide has been shown effective in decontaminating various types of chambers and volumes such as rooms, isolators, processing tanks, and entire facilities, but its use to decontaminate compressed gas piping systems has not been documented. This article discusses using dry gaseous chlorine dioxide (ClO_2) to decontaminate an oxygen (O_2) feed piping system in a pharmaceutical research laboratory and shows that a dry gas can be used to remediate a contaminated piping system.

Bacillus species are Gram-positive, endospore-forming, rod-shaped bacteria found in soil, air, dust, and debris that are quite common in the natural environment. Endospore-forming microorganisms have been found to make up between 5% and 10% of the microflora in a standard cleanroom [1]. Most of these bacteria are considered nonpathogenic and are commonly found in the dust and air of occupied buildings, including cleanrooms. They can enter cleanrooms through poorly filtered air, on clothing, and on incoming materials. Only one endospore is formed per cell and these spores are resistant to heat, cold, radiation, desiccation, and disinfectants, making it difficult to eliminate them from medical and pharmaceutical materials. Because of this, they are a frequent cause of cleanroom contamination.

One option to remove such contamination is to flush the system with a liquid sterilant such as hydrogen peroxide or liquid chlorine dioxide. Both are known to be effective at killing organisms and to kill bacillus spores. Using a liquid sterilant is considered unfavorable because it will introduce moisture into the system; this moisture might linger in the system in dead legs and low areas of piping and can potentially harbor future contaminations. To avoid this, gaseous chlorine dioxide was chosen as the agent because it is a dry gas and can be applied as a dry gas.

CHLORINE DIOXIDE

Chlorine dioxide has been shown to be effective at eliminating viruses [2], fungi [3], bacteria [4, 5], and spores [6, 7]. It has demonstrated inactivation of various toxins and chemicals such as beta lactam [8], anthrax toxins [9], endotoxins [10], pinworm eggs [11, 12], and bed bugs [13]. Chlorine dioxide has demonstrated bacillus spore log reductions in various applications such as rooms [14, 15], suites of rooms [16], isolators [17, 18], tanks [19], electron microscopes [20], ambulances [21], biological safety cabinets [22], and whole buildings and facilities [23–25]. With all these applications, the question still remains: Can it be used to decontaminate piping systems with multiple drops and/or dead legs?

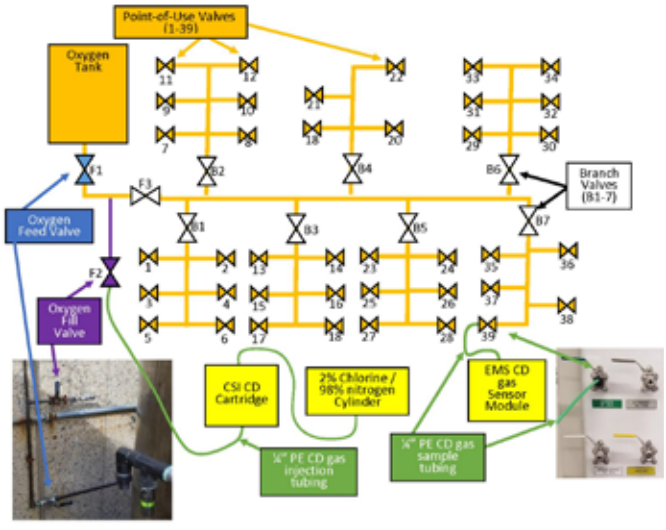
Chlorine dioxide can be generated by various methods and chemical equations. It is not a stable molecule that can be created, bottled, and shipped, so it is typically generated at the point of use. Most chlorine dioxide is generated in solution using acids, sodium chlorite, and water. When it is generated in solution, acidic byproducts that can be aggressive to materials are created. It can also be generated as a dry gas with no byproducts, which allows many materials to be treated with chlorine dioxide with few to no issues.

CHLORINE DIOXIDE GAS EFFECTS

Chlorine dioxide gas has varying effects on materials. In a study [26], several materials were exposed to two cycles of chlorine dioxide gas under vacuum pressure, with 75% relative humidity (RH) and a dosage of 3,350 parts per million (ppm)-hours. The final dosage after two runs was 6,700 ppm-hours. There was no effect on 18-8 or 316 stainless, black oxide, or zinc-plated steel; Buna-N, SBR Black, EPDM, or Viton rubber; PFA, PLGA, PVA, PGA, or liquid crystal polymers; aluminum or zirconium oxide; ETFE or FEP plastic; or vinyl or oil-resistant vinyl (black). There was no effect on aluminum, brass, cellulose ester, copper, epichlorohydrin, gold, Hypalon, magnesium, neoprene, nickel, Nitinol, nylon 6/6, polyglycolides, polyacetals, polylactides, polyester, polyimides, polyketones, polyurethane, Santoprene, silica, or silicone.

There were color changes to butyl, cellulose, cellulose acetate butyrate, fiberglass, latex, natural gum rubber, polyacrylates, and PVF. The following showed color changes and signs of physical

Figure 1: Oxygen piping system decontamination connections.



changes such as oxidation and pitting: bronze, galvanized malleable iron, nickel-copper, silver, and titanium. The material most adversely affected by chlorine dioxide was sorbothane, which demonstrated some disintegration and became very sticky and gummy after the final dosage [26].

DECONTAMINATING A SYSTEM

An oxygen piping system was found to be contaminated with a bacillus strain of organisms at several point-of-service locations, thus requiring decontamination. The oxygen system was fed by an outside tank that feeds 39 points of service stations inside the laboratory. To decontaminate the oxygen system, gaseous chlorine dioxide was injected into the system at high concentrations, > 22 mg/L, and held for 30 minutes. The system was then flushed with oxygen gas to purge the chlorine dioxide gas. The process was successful, as determined by post-exposure swabbing that was found negative for any biological contaminates.

The chlorine dioxide gas generation process used for this process passes a low-level dilute chlorine gas (2% chlorine/98% nitrogen) over solid sodium chlorite, which yields pure chlorine dioxide gas. An additional benefit of chlorine dioxide gas is that it has a color, which allows it to be measured by a photometric device that analyzes certain wavelengths and measures absorbance. This absorbance can then be used to calculate the concentration (mg/L). This allows the process to be tightly controlled and very repeatable.

The typical chlorine dioxide gas decontamination process for spaces is to humidify the target chamber to 65% RH and hold this for a conditioning time. Once that is complete, chlorine dioxide gas is injected in the charging step to reach the target concentration. The typical concentration for rooms is 1 mg/L and for small chambers, such as isolators, it is 5 mg/L. This concentration then sits in exposure until a dosage of 720 ppm-hours is achieved for normal space decontaminations. For example, 1 mg/L for 2 hours of exposure accumulates a dosage of 720 ppm-hours.

1 mg/L ≈ 360 ppm
360 ppm × 2 hrs = 720 ppm-hours

Dosage is the accumulation of concentration over time and with chlorine dioxide gas it is referred to as ppm-hours. Studies have shown that a dosage of 720 ppm-hours at varying concentrations (0.3, 0.5, 1, 5, 10, and 20 mg/L) demonstrated a 6-log reduction of spores [27]. This dosage or contact time, concentration accumulated over time, is based on the conditioning step at 65% RH. Humidity helps condition the spore walls and helps the sterilant achieve its effect [28, 29]. In this application, RH or moisture can be an issue, so it was decided to forgo the RH injection or conditioning step. If steam was injected into the piping system at room temperatures (21°C), condensation would form and introduce unwanted moisture into the system. Previous studies have shown that high concentrations or dosages can achieve log reductions with low RH of 30%-40% [30]. In this study, it was found that a 3,000 ppm-hour dosage achieved a 6-log reduction of spores. The dosage was calculated from the cycle with a chlorine dioxide gas concentration of 100 mg/L for 5-minute exposure.

1 mg/L ≈ 360 ppm
100 mg/L ≈ 36,000 ppm
(36,000 ppm) × (5 min/60 min/hours) = 3,000 ppm-hours

Using this as a criterion, a minimum target dosage of 3,600 ppm-hours was determined for this application. Before arriving onsite to perform the decontamination, it was critical to identify each and every drop or point-of-service location. If any location is missed, then the decontamination might not be successful and the contamination will continue to linger.

MATERIALS AND METHODS

The following materials were used for the study:

- 1 chlorine dioxide gas generator
- 1 CSI chlorine dioxide cartridge
- 1 gas cylinder (2% chlorine/98% nitrogen) with CGA 660 valve
- 2 EMS chlorine dioxide gas sensors on carts
- 6 rolls ¼-inch polyethylene tubing (green)
- 2 ATI PortaSens II low-level sensors, 0–5 ppm
- 2 BSC scrubbers with hoses
- 2 ladders
- Piping distribution system with 39 points of service

The oxygen system is supplied by a 304 stainless steel tank outside the building. The oxygen tank supplies the gas to a 304 stainless steel regulator that reduces the pressure to the operating pressure (50 PSI). This regulator then feeds a copper trunk line, which is made up of 1-inch piping with seven branches that go off to service various stations in the laboratory (see Figure 1).

Each branch has a bronze ball valve (B1–7) to isolate it if necessary repairs/additions are located in a service area. Each point-of-use valve was a 304 stainless steel ball valve located inside the lab. Upon arrival to the site, the first step was to ensure all the point-of-service valves were closed with tubing fittings installed, oxygen feed valve (F1) was closed (to isolate the oxygen tank), and each branch valve was opened. The oxygen tank was not part of the decontamination plan. Once the valve states were verified, the chlorine dioxide gas generator was connected to the system at the oxygen fill valve (F2).

Once chlorine dioxide gas injection connection was made, the oxygen isolation fill valve (F3) was opened to inject CD gas into the trunk. The objective was to fill the trunk with high concentrations of chlorine dioxide gas and then get the gas to each point-of-service valve. To do this, a tube was connected to V39 and bought to the EMS CD gas sensor (see Figures 2 and 3).

After the tube was connected, the valve was opened. V39 is on branch 7 and is the valve the farthest on that branch and farthest from the chlorine dioxide gas injection.

By opening this valve first, the trunk line was filled with high concentrations of chlorine dioxide gas (≈ 100 mg/L). Once the reading at the valve was > 22 mg/L the valve was closed and the next valve was opened (V38). The maximum reading of the chlorine dioxide gas sensor was 22 mg/L, At this point, a second team started the same process by opening (V6), which is the farthest point-of-use valve on branch 1 (B1). Once V6 reached concentration (> 22 mg/L) the valve was closed and V5 was opened. This process was repeated until all point-of-service valves were opened and concentrations measured, and then the vales were closed. After closing the valves, the gas was allowed to sit or expose to achieve the desired kill.

To achieve a target of 3,600 ppm-hours, the exposure time needs to be:
22 mg/L × 360 = 7,920 ppm
(3,600 ppm-hours/7,920 ppm) × 60 min/hour = 27 minutes

Based on this calculation, the target exposure time was set for 30 minutes. After a minimum of 30 minutes of exposure, the oxygen fill valve/gas injection valve (F2) was closed and the oxygen feed valve (F1) was opened. At this time, the tubing from V39 was brought to an exhaust point and the valve was opened. Figure 4 shows multiple point-of-use tubing running to an exhausting biological safety cabinet to remove the chlorine dioxide gas from the piping. Tubing (green) from each point of use was brought to exhausting biological safety cabinets, fume hoods, exhaust point, or scrubbers—this depended on whichever was closest to the point of use valve.

The concentration was then measured using the ATI PortaSens II low-level chlorine dioxide sensor at the tubing exit (see Figure 5). Once the concentration was measured as 0.0 ppm, the line was considered purged and the valve closed and tubing removed, the valve was closed, and the next valve (V38) was opened until the concentrations were at 0.0 ppm.

Figure 2: Connection point and tubing from the point-of-use valve.

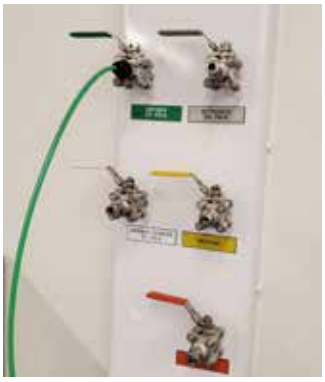


Figure 3: Connection points for EMS sensor.

Figure 4: Removing CD gas from the piping.

Figure 5: ATI PortaSens II aeration measurement.

At this point, the second team brought the tube connected from the point-of-service valve (V6) to an exhaust point, then opened the valve and measured the concentration until the reading was 0.0 ppm. After this the valve was closed and the team moved to the next (V5). This process continued with both teams, until all valves were verified to be completely aerated and measured 0.0 ppm. After this was completed, the chlorine dioxide gas generator and all equipment were removed and packed up, and the facility was exited. The entire process of setup, (connections made; valves opened/closed as needed; chlorine dioxide gas injected, exposed, and gas aerated/removed; and disconnections) took approximately 8 hours.

RESULTS

After the decontamination event was completed, follow-up testing demonstrated the process was successful in eliminating the contamination issue. All swabs taken from several locations showed no growth for any bacillus species. The dosage of each point-of-use valve was calculated by noting the time the concentration was > 22 mg/L and when the concentration was down to 0.0 ppm. This determined the number of minutes that the concentration was exposed at the point-of-use valve. The dosage was calculated using the following equation.

$$\text{Dosage (ppm-hours)} = 360\ \text{ppm} \times 22\ \text{mg/L} \times (\text{number of minutes}/60)$$

The actual minimum dosage in the system was measured/calculated at 6,106 ppm-hours in branch 4. The maximum dosage achieved was 31,723 ppm-hours in branch 1. Branch 1 had the highest dose because this was one of the first sections that chlorine dioxide gas was injected into. Branch 4 was the last section to inject chlorine dioxide gas so it had the lowest overall dosage. No corrosion was noted on any parts immediately after the decontamination or a few weeks later.

DISCUSSION

There was significant variation of dosages within the system. The lowest dosage was 6,106 ppm-hours, whereas the highest dosage was 31,723 ppm-hours. The low dose of 6,106 ppm-hours was much larger than the target dosage of 3,600 ppm-hours. This was easily attributed to lunch (longer than expected). All the gas lines were filled with chlorine dioxide gas and then allowed to sit for minimum of 30 minutes. At this time, lunch was taken and was a little longer than 30 minutes, which accounted for the extra dosage. The large dosage of 31,723 ppm-hours was attributed to it being the line that had the gas in it the longest. This was measured in V6 of branch 1. In this application with the materials used, no corrosion was noted on any parts either immediately or few weeks later after the decontamination. The concentrations in the piping were measured at 22 mg/L.

As noted previously, this was the maximum reading for the EMS chlorine dioxide gas sensor. The actual generation concentration is known to be 100 mg/L, so it can be assumed to be 100 mg/L in the lines. To be conservative, the maximum reading (22 mg/L) was used for all calculations and all assumptions. Additionally, during the purging, several point-of-use valves were opened at the same time. When doing this, the pressure in the system dropped. This necessitated a maximum of four to five point-of-service valves to be opened at any one time to maintain pressure in the system. This was also a contributing factor to the higher dosages in the system. The oxygen supply tank was not part of the decontamination process. It was determined that this was not the source of the contamination, so decontamination of this equipment was deemed not necessary. The oxygen purge to remove the chlorine dioxide gas was the final step of the process.

No follow-up cleanings were done because little to no residues were expected with a dry gas. Studies have shown no detectable residues (chlorine dioxide, chlorite, or chlorate) on potatoes (high organic load) with chlorine dioxide in the gaseous phase [31]. Chlorine dioxide gas does not condense on surfaces and is maintained as a gas through the whole process and as such residues are not expected on hard, nonporous surfaces like a piping system. Little organic load was expected in the process for residues to form, as would be expected with potatoes in the reference given previously.

CONCLUSION

The decontamination service of oxygen piping was successful, as the target dosage of 3,600 ppm-hours was exceeded. More important, it was successful in that there were no follow-up positive swabs for any bacillus strain of organism. The lowest dosage achieved was 6,106 ppm-hours and the maximum dosage achieved was 31,723 ppm-hours. This lowest dosage is 1.7 times the target of 3,600 ppm-hours and 8.5 times greater than the normal dosage to achieve a 6-log reduction (720 ppm-hours). It has been demonstrated that a dry gas can be used to remediate a contaminated piping system.

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AIRASSURE™ PANEL WITH FACTORY-GASKETED EDGE

*Based on laboratory measurements in an approximately 1,000 cubic ft. space with ducted return at pressure difference of 0.020 (in WC). Actual results and savings may vary based on specific room configuration (size, configuration, MEP, pressure, etc.).

Armstrong® CEILING SOLUTIONS