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REGULATORY TRENDS

ICH Q12's IMPACT ON PRODUCT LIFE-CYCLE MANAGEMENT

ISPE Comments to the Annex 2 PIC/S Draft Revision

ISPE Regulatory Steering Council Update

2019 ISPE Global Pharmaceutical Regulatory Summit Report

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REGULATORY TRENDS

12

INTRODUCING ICH Q12: A TRANSFORMATIONAL PRODUCT LIFE-CYCLE MANAGEMENT GUIDELINE

The ICH Assembly endorsed the Q12 guideline, "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management," in November 2019. This transformational guideline has a wide scope of applicability across pharmaceutical drug substances and products (both chemical and biological), drug-device combination products that meet the definition of a pharmaceutical or biological product, as well as both new molecular entities and authorized products.

ON THE COVER Interlocking gears represent the intricacy of the global regulatory harmonization process.

FEATURES

18 ISPE Comments to the Annex 2 PIC/S Draft Revision

Annex 2 is the GMP document by the Pharmaceutical Inspection Co-operation Scheme (PIC/S) addressing manufacture of biological medicinal substances and products for human use. This article shares information about Annex 2 and ISPE's submitted comments to the draft revision of Annex 2 that was released for public consultation in September 2019.

22 Update from the ISPE Regulatory Steering Council

The ISPE Regulatory Steering Council is an advisory group whose primary responsibilities are to develop, prioritize, and reconcile regulatory policy issues through ISPE on behalf of the pharmaceutical industry. This article shares the RSC's latest initiatives and current goals.

24 2019 ISPE Global Pharmaceutical Regulatory Summit: Regulators Address Innovations and Harmonization

At the 2019 ISPE Global Pharmaceutical Regulatory Summit, regulators updated attendees on approaches to industry innovations and the ongoing work on harmonization and reliance around the world.

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30 A GAMP® Approach to Robotic Process Automation

This article introduces the concept of robotic process automation (RPA) and discusses how the technology may be used within a GAMP® framework to support both non-GxP and GxP processes.

34 Wearable Devices and Biometrics to Improve Efficiency in GxP Operations

This second in an ongoing series of articles on Pharma 4.0™ looks at attributability, a core principle in a highly regulated environment that must be constantly respected and is one of the key characteristics for data in the ALCOA+ framework. Wearable and biometric technologies can help ensure attributability in an efficient and compliant way, while also improving other aspects of production.

36 INDUSTRY LEADERS: Mission-Driven Leadership—A Profile of Pam Cheng

In this latest installment in the ongoing Industry Leaders series, *Pharmaceutical Engineering* profiles Pam Cheng, Executive Vice President, Global Operations & Information Technology, at AstraZeneca. In this role, she combines her expertise as an engineer with business savvy and seeks opportunities to lead her company and her industry forward in innovative ways.

DEPARTMENTS

6 MESSAGE FROM THE CHAIR
The Future Belongs to All of Us

10 WOMEN IN PHARMA® EDITORIAL
Mentor Circles: Find the Light, Be the Light

PEOPLE + EVENTS

39 BENEFITING FROM GROWTH OPPORTUNITIES: ISPE BRAZIL AFFILIATE
Brazil's regulatory authority is working hard to make the nation a larger player in the global pharmaceutical market, and these efforts represent opportunities for the ISPE Brazil Affiliate as it undergoes its own transformation.

42 ISPE BRIEFS

59 AD INDEX AND CLASSIFIED ADS

60 END NOTE
Happy Birthday, ISPE

TECHNICAL

43 RISK MANAGEMENT

Good Engineering Practice in Risk-Based Commissioning and Qualification

Over the years, the roles and responsibilities of engineering and quality/validation personnel for commissioning and qualification activities have evolved. Now more than ever, C&Q approaches based on quality risk management principles rely heavily on engineering and the application of Good Engineering Practice to provide documentation for the qualification package.

50 CASE STUDY: PRODUCT DEVELOPMENT

Solubility Enhancement of Ibuprofen by Porous Solid Dispersion Using a Flash Evaporation Method

The solubility behavior of drugs remains one of the most challenging aspects of formulation development and is a key determinant of a drug's bioavailability. This article describes research aimed to improve solubility of a poorly water-soluble drug (ibuprofen) by preparing a porous solid dispersion using a flash evaporation technique.

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By Frances M. Zipp

The Future Belongs to All of Us


Frances M. Zipp

Spring is finally here, signaling a time of new beginnings. Today finds me thinking about International Women's Day (IWD, observed annually on 8 March), a global day of celebrating the social, economic, cultural, and political achievements of women. This year, IWD has the theme of equality, a very fitting theme for the topics I want to share with you. This issue's column is about Women in Pharma® (WIP): their goals, challenges, career advancement, and leadership.

WOMEN IN LEADERSHIP

It's no secret there is a marked disparity in the number of women versus men in leadership roles in the corporate world. According to "Women in the Workplace 2019" [1] (to date the largest comprehensive study of women in corporate America; a collaborative effort of LeanIn.org and McKinsey & Company), based on five years of data from 590 companies:

- Despite progress at senior levels, women remain significantly underrepresented.
- A "broken rung" at the step up to manager is the biggest obstacle women face on the path to leadership.

However, if women are promoted and hired to first-level manager roles at the same rates as men, we will add 1 million more women as managers in corporate America over the next five years.

The study further illustrated that:

- 19% of HR leaders say women are less likely to be promoted to first-level manager roles;
- 7% of men say women are less likely to be promoted to first-level manager roles; and
- 19% of women say women are less likely to be promoted to first-level manager roles.

One of the top solutions companies can introduce to help close the leadership gender gap, the study said, is to provide "mentor groups that bring small groups of employees together for monthly peer support and mentorship." Read on to see how ISPE WIP is making this happen!

WIP GOALS FOR 2020

WIP provides a forum for women in the pharmaceutical industry to connect and collaborate on technical and career advancement topics. You've heard me say I grew up in ISPE, and it's true. Countless colleagues and mentors formed my professional network along the way and helped me become the leader I am today. That's why I'm so passionate about supporting WIP and their efforts to continue fostering balance and progress in our industry.

In a recent blog post on ISPE's iSpeak Blog [2], WIP revealed two ambitious goals for 2020:

- Raising $25,000 for the ISPE Foundation to help professionals of all ages, cultures, and genders to embody the vision and spirit of ISPE with scholarships for educational events and travel grants.
- Developing and sustaining 20 Mentor Circles globally to help more than 200 women and men grow and develop in their career paths. Within the Mentor Circles, there will be discussion of topics that create an environment for members to make themselves vulnerable and break down barriers for the next level of professional and personal success.

Pretty impressive goals, wouldn't you say? Let's reflect on them for a moment. Notice that the first goal aims to raise funding "to help professionals of *all ages, cultures and genders*," and

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the second goal intends to develop and sustain "20 Mentor Circles globally to help 200 *women and men* grow and develop in their career paths."

How is it possible to have a committee for women and also be inclusive? The answer is very simple. As women, we don't tolerate being discriminated against and we also don't discriminate against others. Equal means equal for all. So, here is the distinction: the programming and content are focused on women and will be branded as such, but members of all genders are welcome to participate in ISPE WIP Mentor Circles, meetings, forums, and other events. To preserve the integrity of the WIP brand and mission, only these events can be branded as ISPE WIP events.

MORE AHEAD FOR WIP IN 2020

WIP is rolling out a robust array of events in 2020, including Breakfast Panel Discussion Sessions, Education Sessions focused on professional development, WIP Networking Events, informal meetups, and local Affiliate and Chapter events. In addition, be sure to keep an ear out for the launch of WIP's podcast!

LESSONS LEARNED FROM COVID-19

What I learned over the last few months in dealing with the COVID-19 pandemic:

- *The importance of working together.* In unprecedented numbers, companies in our industry have been working together to solve this complex problem. The willingness of competitors to collaborate for the greater good is a bright point.
- *Know your supply chain and have redundancies if possible.* The potential disruptions in supply of materials, components, and finished goods had some trickle-down effects on our ability to supply critical medicines but was mitigated by proper planning and backups.
- *Contingency plans are important.* Whether plans were needed to allow telecommuting, address travel restrictions, cancel large gatherings, or other issues, the need for contingency plans became paramount, and these need to be factored into our business plans going forward.

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2. Lauria Clark, J. "Women in Pharma®: Goals 2020." ISPE iSpeak blog. 17 January 2020. https://ispe.org/pharmaceutical-engineering/ispeak/women-pharma-goals-2020

Frances M. Zipp is the 2020 ISPE International Board of Directors Chair and President and CEO of Lachman Consultant Services, Inc.

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 By Jeannine Hillmer


Jeannine Hillmer

MENTOR CIRCLES:
Find the Light, Be the Light

Did you know that Women in Pharma® (WIP) has launched a program to initiate Mentor Circles around the globe? While great strides have been made to support women in the workplace, women are still significantly underrepresented in upper management in the pharmaceutical industry. The ISPE WIP Mentor Circle program is a way to promote growing relationships and career development for women scientists and engineers.

The hope is that this will result in higher retention of women and more women in leadership positions in the future. Men are critical to supporting this cause and are encouraged to participate in Mentor Circles.

WHAT ARE MENTOR CIRCLES?

Mentor Circles consist of about 10 women and men who meet four to six times per year either face to face or virtually. These small groups will spend half of their time together networking and the remaining time discussing relevant career advancement topics. To keep things exciting, guest speakers and subject matter experts will be brought in to support the circles. The groups will also be encouraged to network outside of official meetings and use tools such as LinkedIn groups to support career development and relationship growth.

Each group will be a little different, reflecting the needs of people who come together. For example, the Boston Mentor Circle has decided to go with smaller groups of five people called professional "Moais" (social support groups, a popular concept in Japan), and the Midwest is primarily hosting Mentor Circles virtually because the members are geographically dispersed. During this unprecedented time when people are working from home and cannot congregate in groups, virtual Mentor Circles are a great option to stay connected. Ultimately, each Mentor Circle's makeup will differ based on the needs of the group. Watch your local ISPE Chapter and Affiliate publications for surveys of interest to help local volunteer leaders plan their Mentor Circles across the globe.

Mentor Circles have begun at the Boston, Midwest, Seattle, Bay Area, Delaware Valley, and Carolina-South Atlantic (CaSA) ISPE Chapters. There have also been planning discussions with leaders identified for Chapters and Affiliates in San Diego, Los Angeles, Germany/Austria/Switzerland (D/A/CH), Atlanta, Miami, and Singapore. Jennifer Clark, the current ISPE WIP chair, has even started a monthly virtual Mentor Circle within her company, Commissioning Agents, Inc. (CAI). The opportunities to grow your career and help others are plentiful.

Especially during these tough times, it is important to bring light and inspiration to our community.

GET INVOLVED

You can become part of the WIP Mentor Circles by:

- Starting a Mentor Circle in your area or at your company
- Joining a Mentor Circle
- Volunteering to be a guest speaker

Don't think you have time to lead a Mentor Circle? A Mentor Circle Toolkit will help with planning and facilitating your group. It is available at https://ispe.org/affiliates-chapters. Many additional tools are under development.

Especially during these tough times, it is important to bring light and inspiration to our community to enable people to be the best they can be and to help get life-changing drugs to market as quickly and safely as possible. Please email wip@ispe.org with any questions, and to receive support to start your local Mentor Circle.

"We're here for a reason. I believe a bit of the reason is to throw little torches out to lead people through the dark."

—Whoopi Goldberg

Jeannine Hillmer is a Key Account Manager for W.L. Gore & Associates and has been solving engineering, business development, and people problems for 20 years. She has been an ISPE member since 2017.

LeAnna Pearson Marcum's YP Editorial is on hiatus, returning in the July-August issue of *Pharmaceutical Engineering*.

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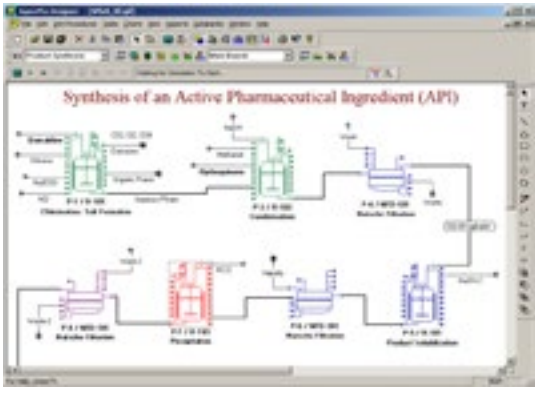

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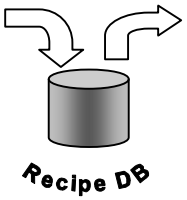

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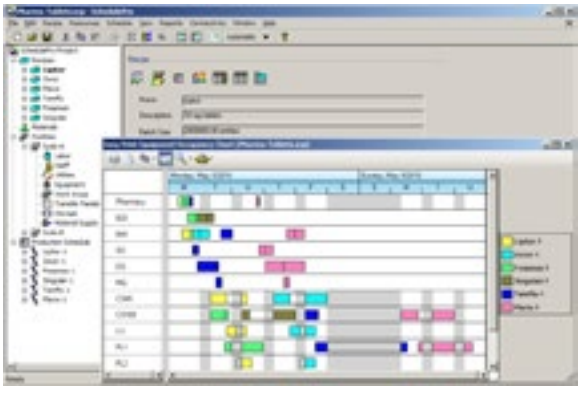

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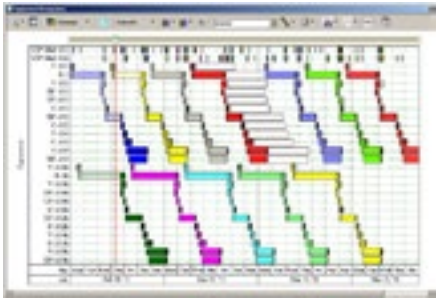

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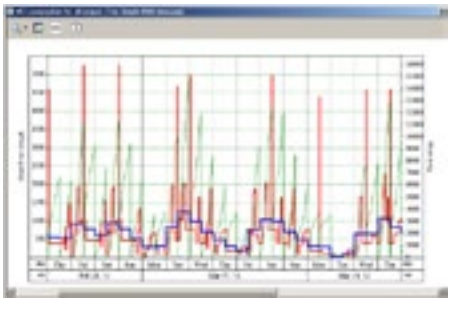
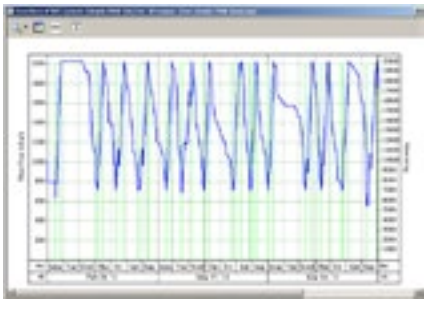


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



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INTRODUCING ICH Q12:
A Transformational Product Life-Cycle Management Guideline

By Eli Zavialov, PhD, Albert V. Thomas, PhD, Saroj Ramdas, Terrance W. Ocheltree, PhD, RPh, and Connie Langer

On 20 November 2019, the ICH Assembly endorsed the Q12 guideline, "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management," at its biannual meeting in Singapore [1]. This transformational guideline has a wide scope of applicability across pharmaceutical drug substances and products (both chemical and biological), drug-device combination products that meet the definition of a pharmaceutical or biological product, as well as both new molecular entities and authorized products.

This article focuses on the final version of ICH Q12, including revisions made after the Step 2 draft was published in 2017. An appendix comparing the Step 2 draft and the final guideline is included in the online version of this article, available at https://ispe.org/pharmaceutical-engineering.

GUIDELINE OBJECTIVES

ICH Q12, which was over five years in the making, builds on the framework established in ICH Q8, Q9, Q10, and Q11 [2–5] and aims to address key remaining technical and regulatory hurdles that prevented the full adoption and realization of flexible science- and risk-based approaches to postapproval chemistry, manufacturing, and controls (CMC) change management during commercial manufacturing.

ICH Q12 defines various tools and approaches to facilitate CMC change management, including in the following sections of the guideline:

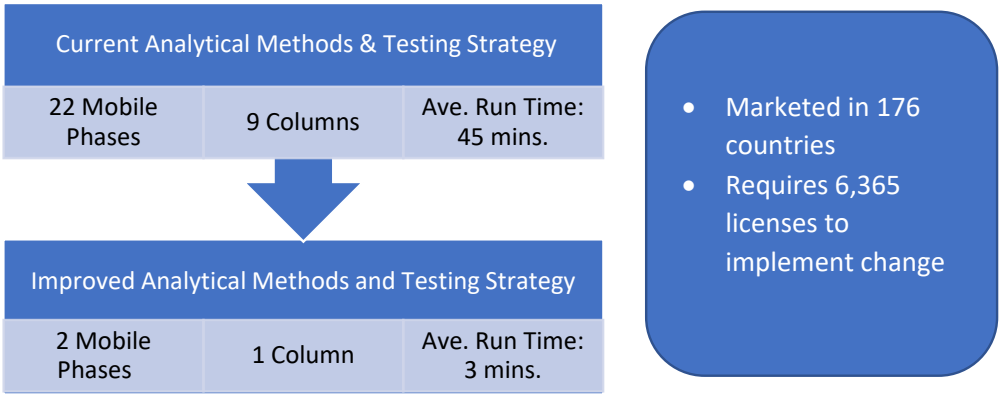
- Established Conditions (ECs)
- Risk-Based Reporting Categories
- Product Lifecycle Management (PLCM) Document
- Post-approval Change Management Protocol (PACMP)

Currently, global regulatory approval of even simple postapproval CMC changes could take more than five years. More complex changes, such as manufacturing improvements and enhancements that could increase product quality assurance, may take longer or might be abandoned if the regulatory burden outweighs perceived benefits. The implementation of ICH Q12 is intended to provide a framework to facilitate the management of postapproval CMC changes in a predictable and expeditious manner, demonstrate how enhanced product knowledge and process understanding improve regulatory flexibility for postapproval changes, and reinforce the importance of an effective change management system through the product life cycle.

Figure 1 illustrates the magnitude of the regulatory burden required to implement an innovative CMC change globally prior to ICH Q12. In the example, an industry central testing lab tests a wide range of different products containing 20 different active pharmaceutical ingredients; this lab would benefit from being able to run its tests using a single efficient "always on" method. The products are sold in 176 different countries, and global implementation of this analytical improvement would require 6,364 licenses [6] and take 10 or more years. Use of ICH Q12 tools such as ECs and PACMPs could drastically reduce the postapproval burden by, for example, reducing the volume of submissions to a single simplified submission to each country for all products; thus, the ICH Q12 tools can facilitate changes globally while maintaining product quality and patient safety.

The original ICH Q12 concept paper was endorsed in September 2014, and the Step 2 draft was issued for public comments in

Figure 1: An analytical example of the magnitude of the global life-cycle management challenge. Reprinted with permission of GSK.



November 2017. During the development process, the ICH Q12 Expert Working Group acknowledged that ICH Q12 was a transformational guideline and it may be challenging for some regions to fully implement all ICH Q12 provisions in a timely manner. The draft version received over 600 consolidated comments and recommendations from regulatory authorities, pharmaceutical industry stakeholders, and various trade groups. All comments and recommendations were considered, and some of this critical feedback resulted in substantial revisions in the final version.

LEGAL DISCLAIMER LANGUAGE

One critical issue was the "opt-out" provision included in the Step 2 draft that stipulated incompatibility of certain ICH Q12 conceptual elements with currently established legal frameworks in several ICH regions. The concepts of ECs and PACMP introduce mechanisms specifically intended to improve regulatory compliance without the need for notification. The proposed "opt-out" provision would therefore have limited the potential global applicability of the guideline, and it would have undermined the fundamental purpose of ICH. Among the various drivers behind this provision, economic reasons relating to the anticipated reduction in the number of postapproval variations and associated user fees were particularly prominent in some regions [7]. Fortunately, these objections were subsequently reconciled. In the final version, the controversial "opt-out" provision was replaced with a recommendation for regulatory members in ICH to clearly communicate the implementation plans in their respective regions to appropriately accommodate the provisions of these concepts in ICH Q12.

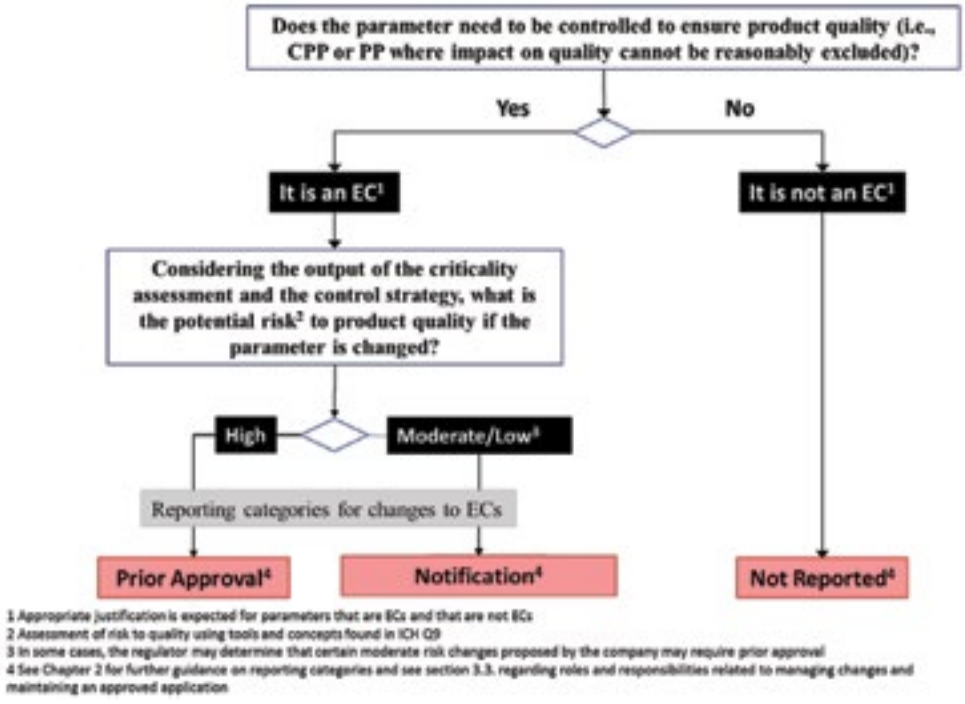
ESTABLISHED CONDITIONS

Another hot topic that elicited many comments was the distinction between the "implicit" and "explicit" ECs as defined in the Step 2 draft. Although the concept of ECs itself was clearly defined as "legally binding information considered necessary to assure product quality," many respondents felt that the further division of ECs into "implicit" and "explicit" categories was redundant and counterproductive because it would likely lead to different interpretations and confusion [8]. Thus, the terms "implicit" and "explicit" were eliminated in the final version, with the added clarification that some ECs with reporting categories may already be defined in the regional legal frameworks, and a market authorization holder (MAH) may use one or more approaches detailed in the guideline to propose their own ECs and reporting categories.

With respect to identification of ECs in the manufacturing process, the Step 2 draft contained a recommendation that ECs include "inputs (e.g., process parameters, material attributes) and outputs (that may include in-process controls) necessary to assure product quality." For manufacturing process parameters, the draft introduced a new key process parameters (KPPs) category, in addition to the familiar critical process parameters (CPPs) category as defined in ICH Q8. KPPs were defined as "parameters of the manufacturing process that may not be directly linked to critical product quality attributes but need to be tightly controlled to assure process consistency as it relates to product quality." A decision tree was provided in the Step 2 draft to further clarify how to identify ECs based on the three criticality-based categories (CPP, KPP, or nonreportable process parameter) and then further assign the appropriate reporting categories based on the level of potential risk to quality (e.g., using the tools and concepts found in ICH Q9).

During the Step 2 draft review and consultations, it became evident that the three-tiered approach to classify the criticality of process parameters has been adopted throughout the industry. However, the proposed definition for KPP introduced the concept of "process consistency," which is not defined in any ICH guidelines. In addition, fundamental provisions of the ICH Q12 guideline indicate that the management of changes impacting process consistency that do not directly impact quality should be managed under the MAH's Pharmaceutical Quality System (PQS). Consequently, the final version of ICH Q12 retained the overall three-tiered approach to process parameter classification (Figure 2), but the reference to

Figure 2: Decision tree for identification of ECs and associated reporting categories for manufacturing process parameters. Reprinted from reference 1.



KPP was replaced with "other process parameters where an impact on product quality cannot be reasonably excluded." As a result, ICH Q12 defined more clearly the scope for the assessment of ECs relative to their impact on product quality. Furthermore, regardless of the approach used, manufacturing process descriptions in Module 3 are expected to remain suitably detailed and to include both ECs and supportive information. These changes in the final version mirror the key provisions from the 2017 EMA guideline on manufacture of the finished dosage form [9].

In the final version of ICH Q12, the discussion of the different approaches available to identify ECs in the manufacturing process was reworked and enhanced to improve clarity. Minimal and enhanced approaches were grouped together as parameter-based approaches because they are primarily focused on the ECs related to process inputs. The performance-based approach was set apart to highlight its primary focus on the ECs related to process outputs. The performance-based approach description was clarified with some additional illustrative examples of the approach's scope of applicability, such as "in-line monitoring of relevant attributes or with feedback controls or optimisation algorithms to achieve the relevant targets for that process step."

PRODUCT LIFE-CYCLE MANAGEMENT

The PLCM document was one of the key tools introduced in the Step 2 draft guideline. It is intended to serve as central repository for ECs and reporting categories and also includes a summary of the product control strategy, PACMPs, and postapproval CMC commitments, as applicable. The PLCM was envisioned to contain a summary of key elements of the product control strategy that justify and explain the selection of ECs. However, in the final version, the summary of the product control strategy was removed to simplify the PLCM document and make it applicable across all ICH regions. In the Step 2 draft, the location for the PLCM document was conspicuously absent, in deference to existing regional/local regulatory requirements. Following critical feedback received during the draft review, the final version of ICH Q12 clarified that the PLCM document should be placed in 3.2.R or for some regions in Module 1 (e.g., Japan). Finally, the final version of the guideline emphasized that submission of the PLCM document is "critical" when an MAH wishes to use any of the ICH Q12 risk-based approaches to define and propose their own ECs with associated reporting categories.

POSTAPPROVAL CHANGES

The chapter on postapproval changes to authorized products was expanded in the final version of ICH Q12 to describe key considerations for structured approaches for some of the more frequent CMC changes, such as analytical method improvements, manufacturing process scale changes and improvements, and alternative packaging components. The detailed example of an approach for analytical procedure changes was moved to Annex II to allow flexibility in updating the example as appropriate. The ICH Q12 Expert Working

Group noted, "The flexibility provided in Annex II may not be available in all regions and in all situations; some specific changes may require prior approval as defined in regional guidance." Specific guidance on the type and amount of stability data expected to support postapproval changes was given its own chapter.

PACMP is a regulatory tool providing prospective transparency and expectations for regulatory reporting categories for specific postapproval changes. PACMP has been an integral ICH Q12 concept throughout the guideline's development and must be approved by regulatory authorities. With the implementation of ICH Q12, PACMP can help ensure robust change management globally by providing a consistent approach to regulatory reporting categories across ICH regions.

ICH Q12 ANNEX

Between Step 2 and Step 4, the ICH Q12 Annex documents were also revised and updated [10]. The examples provided in Annexes IA and IB on how to identify ECs in the manufacturing processes of chemical and biological products were reduced to focus on fewer individual process steps. However, the justifications substantiating these examples were significantly expanded to provide increased understanding and practical implementation of these concepts across all three risk-based approaches provided in the guideline. Annex IC was added to specifically illustrate how ECs can be identified for analytical procedures, using as an example capillary electrophoresis for a biological drug substance under minimal development approach. The examples of PACMPs for chemical and biological products were moved into Annexes ID and IE, respectively, but otherwise remained largely unchanged. An example of a PLCM document, with a few important clarifications based on public comments, was moved into Annex IF. The revised example is not an exhaustive list of all ECs that may be included in an application; it serves only as an illustrative example for manufacturing process-related ECs for a small molecule drug. A comprehensive list of all Common Technical Document (CTD) sections containing ECs is provided in Appendix 1 of the main guideline.

As mentioned previously, Annex II of the final guideline contains the detailed example of a structured approach to analytical procedure changes.

CONCLUSION

The adoption and implementation of ICH Q12 principles is expected to transform the global regulatory environment by leveraging the risk- and science-based concepts of Quality by Design articulated in ICH Q8, Q9, Q10, and Q11. ICH Q12 should drive regulatory convergence for postapproval changes and enable continual process improvement and the adoption of innovative technologies that increase quality assurance and reduce the

Appendix: Detailed Table of ICH Q12

An appendix to this article comparing the Step 2 draft of ICH Q12 and the final guideline is included in the online version of this article, available at https://ispe.org/sites/default/files/pe/2020-issues/2020-pe-may-june-appendix-summary-ich-q12-step-2-to-step-4.pdf

volume, time, and resources needed to prosecute regulatory applications. The use of ECs provides clarity and improves transparency between regulatory authorities and industry. PACMP should improve clarity for verification, documentation, reporting, classification, and implementation of CMC postapproval changes. ICH Q12 encourages the industry to embrace the new paradigm to prospectively consider and assess process and product improvements and innovations by using the new tools and approaches to expedite regulatory assessments and inspections.

The implementation of ICH Q12 may warrant increased interactions between industry and regulatory agencies in the short term. However, the long-term expectation is that use of ICH Q12 will decrease the need for postapproval filings and agency interactions. The initial interactions may take many forms, ranging from product-specific meetings to open forums. ICH intends to develop additional training materials, which should be beneficial to both the industry and regulators.

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ISPE COMMENTS
to the Annex 2 PIC/S Draft Revision

By Jean-François Duliere

This article was written by Jean-François Duliere on behalf of the full ISPE Comment Lead Team Annex 2 PIC/S: Jean-François Duliere, Richard Denk, Ylva Ek, Alice Redmond, Nuha Al-Hafez, Maria Amaya, David Estape, Oliver Kurz, Vincent J. Cebular, Erich Bozenhardt, Martin Erbo Jensen, Thomas Zimmer, Bruno Dalle, Morad El Gueddari, Charlotte Kornbo, and Donata Canobbio

ISPE Regulatory Advisors: Robert W. Tribe and Christopher N. Potter, PhD

Annex 2 is the Good Manufacturing Practices (GMP) document by the Pharmaceutical Inspection Co-operation Scheme (PIC/S) addressing manufacture of biological medicinal substances and products for human use. This article shares information about Annex 2 and ISPE's submitted comments to the draft revision of Annex 2 that was released for public consultation in September 2019.

The Pharmaceutical Inspection Co-operation Scheme (PIC/S) was created in 1995 to be a nonbinding formal cooperative arrangement among regulatory authorities in the field of Good Manufacturing Practices (GMP) of medicinal products for human or veterinary use. The PIC/S had 53 members as of January 2020. The PIC/S objectives are to harmonize inspection procedures worldwide. This is reflected in the PIC/S mission: "Lead international development, implementation and maintenance of harmonized GMP standards and quality systems of inspectorates in the field of medicinal products" [1].

The draft revision of Annex 2 issued for public consultation is divided into two parts:

- Annex 2A for Manufacture of Advanced Therapy Medicinal Products for Human Use
- Annex 2B for Manufacture of Biological Medicinal Substances and Products for Human Use

The revision of this document was required to take into account the international development in the regulation of advanced therapy medicinal products (ATMP), with particular attention to the new European Commission guideline on GMP for ATMP [2], while addressing at the same time concerns of PIC/S Participating Authorities with regard to patient safety and proportionate regulation for ATMPs. Draft Annex 2B is the revised version of EU Annex 2 for biologics (excluding ATMPs).


Jean-François Duliere

FOCUSED CONSULTATION

The commenting period was from 20 September 2019 to 20 December 2019. Organizations and companies were asked to submit their comments to six predefined organizations; ISPE was one of them. The PIC/S has structured the consultation around specific questions and allowed for additional comments on a line-by-line basis. During the commenting process, ISPE had the opportunity to discuss directly with the PIC/S the new annex, which facilitated more precision when answering the questions.

The comments submitted by ISPE members, Affiliates, Communities of Practice (CoPs), and pharmaceutical companies through their members were collected and consolidated by the ISPE Comment Lead Team for Annex 2 appointed by ISPE.

After 20 September 2019, the team compiled all received comments and started a short period to review all the comments from 23 December 2019 to 6 January 2020. This was a strong effort. During this period, the team had a two-hour conference call every two days to check the questions' answers and check the comments line by line. The team made a great effort to comply with the due dates. The final review and approval have been made by the team's regulatory advisors.

COMMENTS

In this article, we reproduce the questions from PIC/S and the answers provided by ISPE. They are the main body of the consultation and address the most significant aspects. The ISPE Comment Lead Team sees this focused consultation process to be of high value and a good example to follow in the future. This structured way of commenting on a regulatory document helps to focus and consolidate the key view of industry stakeholders and should facilitate the next steps of the revision process.

Question #1: Scope of Guidance Document

What are your views on ATMP guidance applying to the manufacture of ATMP products as described in the following illustrations (line 58 of the consultation document)?

As an alternative, should plasmid manufacturing and/or virus manufacturing be in scope of this document, if yes in what form?

ISPE Answer

As ATMP's materials are not covered by the ICH Q7 Guide, the EU GMP Part II or the PIC/S GMP Guide Part II, we consider these materials need to be part of revised Annex 2 PIC/S Part A. We suggest the proposed extension to virus and plasmid could be incorporated, as well as mRNA.

The document should, however, address these materials (virus, plasmid, mRNA manufacturing) in a flexible way to allow for new starting materials that emerge in the future to be included in the scope without requiring a new revision of the document.

The increase of GMP requirements as the production steps come closer to the finished product is good and needs to be retained as a principle.

We suggest to split the table in a different way, with one part dedicated to Drug Substances and another part dedicated to final product manufacturing, formulation, and filling. This could incorporate different levels of requirement of GMP.

We suggest adding an arrow below the table to show the increase of GMP requirements following the processes steps coming closer to the final steps.

We suggest as well to have Annex 2A linked with PIC/S GMP Part II (ICH Q7A).

We propose having a separate Establishment of MCB and WCB with appropriate level of GMP requirements box and not positioned as they are in the table.

Question #2: Product Quality Review in Clinical Trial Phases

Considering the length of time that some advanced therapy investigational medicinal products (ATIMP) could be in clinical trial phase, is there a need to include requirements to periodically perform a Product Quality Review proportionate to the development stage? Currently, product quality reviews are not required for medicinal products in a clinical trial phase. Expectations for a Product Quality Review for ATIMP could consider aspects found in Section 1.10 of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part I Chapter 1 Product Quality Review. This could include ...

ISPE Answer

For this section, we consider that clause 1.4 of Part 1 of GMP PIC/S is more appropriate, rather than clause 1.10.

A full quality review as per marketed products seems not to be desirable, which is consistent with the approach for clinical products. Nevertheless, based on QRM principles, a review of quality information from previous batches and previous steps would be useful. Trend analysis requiring more data information should not be required.

This review should consider points i, ii, iii, iv, v, vii, ix, xi, & xii of section 1.10 of the PIC/S GMP Guide Part I, as these points need to be part of the manufacturing preparation to keep production under control. We suggest to remove from the new section 1.10 for ATMPs at the clinical stage points vi, viii, x, which are not relevant for these products at the clinical stage of development.

The following steps under QRM should be adapted to the stage of product development: The premises and equipment used for clinical trials should be qualified. Due to potential low manufacturing activity, inspection or checking of facilities and equipment should be performed at appropriate intervals. Production should be verified in a continual way by examination of increasing amounts of in-process data to keep the process under control without having a full process validation.

Question #3: Working Environment Requirements when Processing Is not Performed in a Closed System

What are your views on the expectation for the working environment requirements when processing is not performed in a closed system? Section 3.13 of the attached consultation document for Annex 2A presents a PIC/S proposal. These expectations align the same requirements expected for the manufacture of sterile medicinal products but allow for an exception based system if authorised by the competent authority.

You may need to make reference PIC/S PE 009-14 PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 1 Section 1 to 35. Please note that Annex 1 has recently concluded a consultation and is currently being revised.

ISPE Answer

It is not necessary for all ATMPs to be manufactured under sterile conditions. If the products can be sterilized after a process step, less stringent conditions can be applied. If the product cannot be sterilized, then more environmental verification should be carried out at the most critical parts of the process.

When processes are made in a non-closed system, it is appropriate to refer to Annex 1 GMPs for the parts relevant for ATMPs with respect to particle count, bacteria count, airflow checking. Air classification should be defined following QRM and CCS (Contamination Control Strategy) principles. Based on CCS, the

When a product is intended for a life-threatened product, with no manufacturing alternatives, then with NCA's agreement less stringent conditions should be acceptable based on QRM reviews and CCS principles.

appropriate level of air classification should be determined having regard to the specific risks, taking into account the nature of the product, its relevant critical quality and safety attributes, and the manufacturing process step. We suggest keeping reference to Annex 1 parts relevant to ATMPs even with the future release of the revision of this document.

When a product is intended for a life-threatened product, with no manufacturing alternatives, then with NCA's [National Competent Authority's] agreement less stringent conditions should be acceptable based on QRM reviews and CCS principles. These production conditions need to be defined before approval, and additional environmental verification at the most critical point should be made during production to demonstrate that the product and the patient are not at risk.

Question #4: Equipment Use when Manufacturing Extends into Hospitals

What are your views on the expectations to address facilities and equipment used in a hospital ward or theatre? Section 3.14 of the attached consultation document on Annex 2A presents a PIC/S proposal when certain manufacturing activities must be extended into hospitals as part of decentralized or point of care manufacturing.

You may need to make reference PIC/S PE 009-14 PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 15 on Qualification and Validation or Annex 20 on Quality Risk Management.

ISPE Answer

Performing production steps in premises that are not under direct control of the MAH [Marketing Authorization Holder] or Sponsor environment should be approved by Competent Authorities as part of the process. The MAH needs to keep under control those process steps for which it has direct control, and ensure equipment has been verified using Annex 15 recommendation as support (PIC/S Annex 15 will be considered a support documentation). Responsibility for assuring the quality of the manufacturing supply chain remains with the MAH.

Manufacturing steps performed in premises that are not under direct control of the MAH or Sponsor environment such as a hospital ward or theatre should be carried out under a recognized Quality System. Premises and equipment if not qualified should be verified following hospital equipment and premises verification rules bringing to the installations the appropriate level of confidence for the intend use. We suggest making GMP Annex 15 a non-mandatory document, and used only as a support document.

Question #5: Batch Release when Product Does not Comply with Specification

What are your views on the expectations specified when release of a batch may be in a patient['s] best interest but it does not comply with specification? Section 5.45 and 5.46 of the attached consultation document on Annex 2A present a PIC/S proposal.

ISPE Answer

As indicated in the proposed text, connection between the treating physician and Authorised Person of MAH or manufacturer is a critical point, especially when a batch not complying with its release specification is proposed for administration. The Authorised Person should be consulted to provide input to the treating physician's risk assessment. However, the sole responsibility for administering the treatment rests with the treating physician.

Even in a PIC/S document, we suggest clarifying the Notification to the Competent Authorities in Europe, which requires 3 Authorities to be informed (Supervisory Authority in EU and EMA + National Competent Authority). This could be a note in the document.

Question #6: Batch Release in Cases of Decentralized or Point of Care Manufacturing

What are your views on the expectations to address batch release when certain steps of manufacturing are decentralized or occur at the point of care? Section 5.47 and 5.48 of the attached consultation documents on Annex 2A present a PIC/S proposal.

ISPE Answer

Data collection, data management, data integrity, and delegation of responsibilities related to batch release for such a complicated supply chain is a critical point. Batch release processes and responsibilities need to be fully explained, understood, and documented particularly as batch release may be carried out under electronically shared data. For such products if there is a short shelf life, the release review should be done in a shorter time frame than one month as proposed as example based on QRM if many other batches have to be produced and released in the organization. All

listed items in 5.48 seem acceptable and cover all activities under Authorised Person and MAH responsibilities.

All Quality assessments and contracts need to be ready before starting such a batch certification and release process.

Question #7: Starting Material

What are your views on the control of starting materials? Is the approach to control of starting materials sufficiently described in the draft PIC/S *Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use* (Sections 5.24 to 5.33, B1.3 to B1.4, B2.1 to B2.2, and B3.3) when read with other applicable sections of PIC/S Guides or are there any requirements or positions that need to be accounted for with particular reference to critical starting materials, raw materials and active substances?

ISPE Answer

Some active ATMP materials are coming from patients or donors; it needs to be emphasized that the sampling of these materials should be undertaken in a way that will not contaminate the material. Also, the supply chain must allow product transfer without damage to the product.

Application of QRM to the total supply chain QRM is a critical part of the process to understand the risks to raw material quality. The guidance could be enhanced with a short explanatory paragraph of the importance of QRM across the whole supply chain.

We suggest adding a definition of "Raw Materials for ATMPs" in the glossary.

Question #8: Outsourcing to Non GMP Licensed Third Party in Exceptional Circumstances

What are your views on the expectations that provide flexibility to ensure that specialised testing and collection of human starting material is adapted to the particularities of ATMP while still maintaining the necessary quality of the product and reliability of testing as applicable? Section 7.1 of the attached consultation document on Annex 2A presents a PIC/S proposal.

You may need to make reference PIC/S PE 009-14 PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 15 on Qualification and Validation or Annex 20 on Quality Risk Management

ISPE Answer

We suggest not mixing starting materials collection and specialized testing. Both can be carried out in non-GMP environments. Nevertheless, special care has to be taken for material sampling as material will be processed in GMP environments and sampling must not bring contamination to patients. The human starting material collection should be performed according to the national laws on donation of cells and tissues for clinical purposes. A full traceability management needs to be developed.

Even with non-GMP testing laboratories, the equipment and conditions should be commissioned and the laboratory should have procedures and a robust quality system, for example as per ISO 9000 standards. In any case, the MAH is responsible of the work done by its subcontractors. Release cannot be delegated.

Question #9: Other Considerations

Is there any other considerations related to GMP for the manufacture of ATMP that you deem important that is not covered by these questions? If so please provide feedback, limited to your top two priorities.

ISPE Answer

We suggest clarifying in the scope of the document or in the Principle section the links between ATMPs GMPs, and Annex 1 when revision is finalized. As ATMPs for some processes do not need to follow aseptic manufacturing, Annex 1 application should be considered based on QRM linked with the processes steps and not applicable as per aseptic processing given in the draft Annex 1.

1. QRM principles should be enhanced in the document, for example by including a paragraph in the Principles section to cover all the document even in the parts where it is not mentioned. It is recognized that QRM is mentioned in section 1.3.

2. Software validation should be addressed either in the Principles or Validation section since some practices will require IT communication between production sites.

CONCLUSION

After this work, the Comment Lead Team wants to thanks all Chapters and Affiliates, COPs, and members for their participation to this PIC/S consultation to industry. The work and effort to answer the specific questions regulators asked industry stakeholders have been very interesting and should contribute to develop the PIC/S thinking in this rapidly developing industry to establish harmonized international GMP standards.

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UPDATE FROM THE ISPE Regulatory Steering Council

By Roger Nosal and Sarah Pope Miksinski, PhD

Virtually every ISPE member has at least one story to tell about how health authority inspections or the review and approval of regulatory applications have affected their efforts to supply critically needed medications to patients globally. Although these stories may emphasize the considerable challenges that ISPE members face, they also frequently identify great opportunities for innovation and collaboration with health authorities. The ISPE Regulatory Steering Council (RSC) aims to help the pharma industry capitalize on these opportunities.

Many of the dynamic challenges facing the industry are unanticipated regulatory issues. The pharmaceutical industry is among the most regulated business sectors, and the bar for approval of regulatory applications has steadily risen as knowledge of chemistry, manufacturing, and analytical technology has expanded. Inspection scrutiny has extended beyond confirmation of commercial readiness and evaluation of quality systems and is now concentrated on process parameters and manufacturing sustainability. In addition, unprecedented globalization, which has introduced new market opportunities, has contributed to the emergence of complicated and precarious supply chains that attract increased regulatory concern. When seeking to build an effective supply chain for global markets, stakeholders managing diverse globalization efforts face divergent and often variable regulatory expectations across the many different regions where they operate.

Since its inception in 1980, ISPE has invited regulators to participate at conferences so attendees can learn about industry innovations and share perspectives on the global regulatory landscape. Over the years, this knowledge exchange evolved and expanded to address emerging quality issues as a concerted, prospective, and deliberate objective. With the advent of accelerated development and scientific and technical innovations, new regulatory policies were proposed through ISPE's Pharmaceutical Quality Lifecycle Implementation® (PQLI®) initiatives as accommodations to fundamental regulations and regulatory precepts. Although the focus on pharmaceutical technology remains a primary motivation for ISPE outreach to regulators, patient-centric quality initiatives with particular emphasis on improving submission and assessment efficiency also warrant effective engagement and significant collaboration between industry and regulatory authorities.

RSC'S ROLE AND PRIORITIES

In early 2017, the ISPE International Board of Directors authorized the establishment of the RSC, a strategically focused advisory group with primary responsibilities to develop, prioritize, and reconcile regulatory policy issues through ISPE on behalf of the pharmaceutical industry [1]. The RSC's role is to:

- Provide regulatory advice and strategic direction for ISPE
- Cultivate partnerships with regulatory authorities and provide an effective forum to address and reconcile regulatory policy and global harmonization issues
- Connect, align, integrate, and prioritize ISPE regulatory strategies

The RSC serves as the strategic regulatory arm on behalf of the ISPE International Board of Directors. Under this umbrella, the Regulatory Quality Harmonization Committee (RQHC) and PQLI® identify, develop, research, and issue industry positions, responses, and guidelines to regulatory concerns. The current list of ISPE regulatory priorities includes the following topics:

- Annex 1: Input on revision to the European Commission
- Cell and gene therapy
- Continuous manufacturing
- Drug shortage prevention:
  - Business continuity management plan
  - Communications with health authorities

- ICH Q12
- Patient-centric quality standards
- Personalized/mobile manufacturing
- Pharmaceutical quality:
  - Quality maturity framework
  - Cultural excellence
- Pharmacopoeia harmonization
- Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP inspections mutual reliance
- Process validation

The RSC recommends a limited number of regulatory priorities to the ISPE Board, and, on occasion, it has assessed additional contemporary regulatory issues on behalf of or in collaboration with other industry leadership organizations. The RSC is currently discussing two initiatives—mutual reliance for inspections and pharmacopoeia harmonization, which were prompted by the Global Pharmaceutical Manufacturing Leadership Forum (GPMLF)—to determine ISPE's appropriate role and its capacity to provide support, industry metrics/impact analysis, and training on behalf of industry.

ADVANCING INDUSTRY-REGULATOR COLLABORATION

Recently, several efforts focused on regulatory efficiency have been proposed through issuance of multiple regulatory guidelines globally. Among the innovative initiatives are Knowledge Assessment and Structured Application; Pharmaceutical Quality/Chemistry Manufacturing and Controls; and the multi-region assessments (Mutual Recognition Agreements, Mutual Reliance Initiatives, Australia, Canada, Singapore, and Switzerland consortiums, etc.). Regulators are recognizing that the efficiency of their application reviews must improve to get medicines to patients faster and with improved quality assurance. However, the need for improved global convergence and harmonization of standards is often at odds with efforts to increase assessment efficiency.

Across the global landscape, there is also a critical gap between regulatory efficiency, patient-centricity, and global harmonization; this gap becomes very visible when discussing supply of products to the patients who need them. On the one hand, improved assessment efficiency may positively benefit certain health authorities but consequently impose inefficiencies on industry. On the other hand, increased submission efficiency may assist industry but introduce challenges to health authorities in their respective assessment paradigms. In both cases, the "efficiency" strategies may compromise the expediting of important medicines to patients. The RSC believes a collaborative approach among members from regulatory authorities and industry is most conducive to improving effective efficiencies that accommodate the unique accountabilities of both regulatory and industry partners. Patient-centric motives should be paramount for all stakeholders, and any strategic efforts should be rooted in a collective understanding of and respect for the relevant similarities and differences between regulators and industry.

Patient-centric motives should be paramount for all stakeholders.

ISPE has a crisp, clear, and comprehensive vision statement that includes regulatory strategy as a collaborative endeavor:

> *Provide solutions to complex pharmaceutical industry challenges through manufacturing innovation, member and workforce development, technical, regulatory, and compliance collaboration.*

CONCLUSION

Through the strategic assessment from the RSC, ISPE is continuing its focus on priority initiatives that are important to industry; these initiatives will resonate even more when developed via alignment and strong collaboration with regulatory authorities. Though this approach provides clear benefits for both regulators and industry, the most significant benefits will be realized by patients worldwide.

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About the authors

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2019 ISPE Global Pharmaceutical Regulatory Summit

REGULATORS ADDRESS INNOVATIONS AND HARMONIZATION

By Susan Sandler

At the 2019 ISPE Global Pharmaceutical Regulatory Summit, regulators updated attendees on approaches to industry innovations and the ongoing work on harmonization and reliance around the world.

The conference, held on 5–6 December 2019 in North Bethesda, Maryland, included sessions on many regulatory-related topics. Here are some of the highlights from regulatory presentations and panel discussions during two plenary sessions on 6 December.

REGULATORY AND INDUSTRY INNOVATIONS

The first plenary, "Regulatory and Industry Innovations," featured panel members from the US FDA Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) emerging technology initiatives. Christine Moore, PhD, Global Head and Executive Director, GRACS CMC Policy, Merck & Co., Inc., was the session leader.

CDER and ETT

Sau (Larry) Lee, PhD, Director and Emerging Technology Team Chair of CDER's Office of Testing and Research, shared insights into the CDER approach to pharmaceutical innovation, especially in the chemistry, manufacturing, and controls (CMC) area. CDER wants to facilitate and promote pharmaceutical innovation and established the Emerging Technology Program, led by the Emerging Technology Team (ETT), to achieve this end. ETT has a centralized focus and is a collaborative platform in the FDA and between the FDA and the pharma industry.

ETT is a cross-functional team with representation from all relevant FDA areas: the Office of Pharmaceutical Quality (OPQ) and the Office of Compliance (OC), which are both part of CDER, and the Office of Regulatory Affairs (ORA). All team members have extensive experience in review, and many also have extensive experience in industry, which Lee noted is very important for working with reviewers, investigators, and the industry. The team can also recruit subject matter experts from other FDA offices as needed.

ETT addresses development, manufacturing of technology for generic, biological, and biosimilar products. Another initiative is pursuing harmonization by engaging with international agencies to facilitate/ share information.

Lee noted that ETT will be involved in the entire application/ evaluation process, starting with presubmission meetings. "The best way to learn the technology is to see it, and we need to work with industry to ask relevant questions and see the technology." ETT is also involved in integrated quality assessment (application review and preapproval inspection). Continual involvement of ETT members throughout the process is very important, Lee noted, because it helps avoid inconsistency in evaluation of emerging technology and minimizes the risk of giving inconsistent recommendations to the industry.

Lee pointed out that early engagement can even start without an identified drug candidate, which is very different from the

investigational new drug (IND) process. There is no prescriptive process for emerging technology, but the sponsor must justify how the proposed technology meets two criteria: pharmaceutical novelty and product quality advancement.

Lee suggested that companies preparing for an ETT meeting should "be transparent and willing to share with the agency early. Don't be afraid to get and answer many questions," he said. The goal is to achieve a common understanding and to see regulators as part of the team.

Lee stressed that the FDA is willing to learn. It wants to understand and recognize the potential of new technology with an open mind, make science- and risk-based assessments and decisions, and be transparent to the industry. To that end, the agency is not afraid to ask questions and is taking a multidisciplinary, collaborative approach to emerging technology. Lee noted that feedback from current and past participants has indicated high overall satisfaction ratings on value, process, and awareness in working with ETT.

For further information on ETT, Lee directed attendees to two FDA guidance documents: "Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization Guidance for Industry" [1] and "CDER Manual of Policies and Procedures (MAPPs)" [2]. He said these documents explain what ETT is and offer more specifics about sponsor processes to engage and get early feedback from the FDA.

CBER and CATT

Manuel Osorio, PhD, Senior Scientist for Emerging Technologies and Medical Countermeasures, CBER Advanced Technologies Team (CATT), spoke on "Advanced Manufacturing of Complex Biologics: A CBER Perspective." He shared information about CATT, the new CBER team addressing emerging technologies.

He noted that CBER agrees with many of the messages from Lee's presentation: both CDER and CBER are committed to developing new technologies. However, there are also differences between CATT and ETT, Osorio said. CBER focuses on complex biologics, and CATT works with advanced manufacturing technologies, including 3D bioprinting, continuous manufacturing, cell culture systems supporting large-scale or rapid production, and monitoring/measurement technologies.

According to Osorio, challenges in cell and gene therapy include the lack of capacity for manufacture of lentiviral and adeno-associated virus vectors, which is limiting clinical development. Also, the process of production in current cell lines is still not able to meet demand. CBER is committed to supporting research and collaborating to try to address these issues, he said. For example, modernizing vaccine production by including advanced manufacturing technology could improve agility to respond to pathogens.

"Early engagement for new therapies is very critical," Osorio said. "It provides the way for us to learn about new approaches and for industry to minimize risks of implementing new manufacturing technologies." About 18 months prior to the conference, CBER

Panel members for the first plenary session: Manuel Osorio (left) and Sau (Larry) Lee.

created the Initial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) Program [3, 4] for potential sponsors to engage early with CBER staff and receive their input. The input is nonbinding, and the early-stage development communications replace the "pre pre-IND meeting." The purpose of INTERACT meetings is to have important product-specific discussions about CMC, pharmacology/toxicology, and clinical issues, he said. These talks precede the pre-IND phase or the formal regulatory advice phases. (See reference 3 for more information on the INTERACT Program.)

Created in June 2019, CATT includes members from each review office in CBER; most team members are division/office directors or deputy directors. The team prioritizes building internal science and regulatory expertise and promoting the creation of modernized domestic manufacturing.

The scope of requests to CATT from prospective developers of novel therapies includes innovative approaches to biologic development, such as novel technologies that can significantly impact product development, as well as manufacturing process and control strategies with potential regulatory implications. When a request is received by the INTERACT program, a monthly work group meeting discusses the submission and decides how to address it and respond. The response may be an email or a meeting invitation, depending on whether the request is about a novel technology and if CATT has the resources to address it.

Osorio emphasized that the FDA is building internal science and regulatory expertise by developing and supporting the CBER research program, hiring new principal investigators to develop research projects and regulatory expertise, and hiring additional full-time reviewers. CBER also is establishing an advanced technologies seminar series and hosts academic and industry experts in advanced manufacturing technologies, who come to the FDA campus to educate the staff.

CBER is promoting the creation of modernized domestic manufacturing through CBER grants and contracts to support research projects studying improvements for advanced manufacturing of

Having partners for inspections lets the FDA focus on other high-risk areas.

biological products. Funded research addresses knowledge and experience gaps identified for emerging manufacturing and testing technologies and supports the development and adoption of such technologies in the biological product sector. To date, CBER has awarded about $12 million to support research outside of the FDA.

Ongoing CBER initiatives include keeping pace with advancing technologies, refining the regulatory framework as necessary, overcoming limits in manufacturing, collaborating in the US and internationally on initiatives such as ICH Q13 and harmonized guidance on continuous manufacturing, and facilitating optimal product development.

CATT and ETT will meet quarterly to share information, Lee said, and Osorio noted manufacturing at point of care is the first topic to be addressed, as it affects both CDER and CBER.

GLOBAL RELIANCE AND HARMONIZATION

The closing plenary of the conference, "Global Reliance and Harmonization," included presentations from FDA and United States Pharmacopeia (USP) representatives followed by a panel discussions among presenters and other regulators. The session leader was Søren Pedersen, PhD, Senior Director, External Affairs, Quality Intelligence and Inspection, NovoNordisk A/S. In introductory remarks, he noted the great importance of regulatory convergence, but also reminded the audience that many efforts remain fragmented and uncoordinated: duplicate GMP inspections, many different GMP requirements, many different pharmacopoeias, different registration dossiers, and postapproval change differences, just to name a few.

MRAs

Mutual recognition agreements (MRAs) are one approach to eliminating duplication and increasing input from the partnering regulatory organizations. Alonza Cruse, Director, Office of Pharmaceutical Quality Operations, ORA, FDA, presented on "The Impact of the US-EU MRA on Pharmaceutical Inspections" and other FDA actions to increase harmonization.

Cruse spoke about changes within the FDA itself in recent years, including improved consistency and transparency of inspections, providing decisional letters to inspected facilities with classification about the inspections, and looking to shorten time frames where enforcement or other actions have to happen so that such actions occur rather quickly.

The FDA is seeking to harmonize standards and work cooperatively with industry, academia, and regulators around the world, Cruse said. The MRA between the FDA and the EU is one action toward that goal. Implemented on 1 November 2017, it allows reliance by drug inspectors on information from their respective drug inspection authorities (FDA and EU). As of July 2019, 28 EU countries were participating (with provision for a stand-alone US-UK MRA after the UK left the EU). In addition to the MRA with the EU, the FDA may use inspection reports from other regulatory bodies in certain circumstances, usually when a US State Department warning has been issued or another event prevents FDA inspectors from physically visiting a facility.

Cruse described how the FDA interacts with partners on inspection reports, including the site selection inspection list generated for foreign and domestic sites. When the list comes, FDA checks all MRA countries on the list for any recent inspection or an inspection done within a close time frame, and if there is a report for translation and review that is similar to what would be done in an FDA-generated report. Having partners for inspections lets the FDA focus on other high-risk areas, Cruse noted.

The FDA reviews inspection reports because it is responsible for suitability of drugs intended for US patients, and it uses EU reports just as it uses FDA inspection reports to evaluate conformance with GMP. The reports help the FDA assess applications for marketing new drugs, determine a site's overall state of quality, and identify risks to drug availability. The FDA is evaluating whether to extend MRAs beyond human drugs to cover veterinary drugs as well. This could increase collaboration, Cruse said.

PIC/S

The FDA is also working across borders on regulatory harmonization within the Pharmaceutical Inspection Co-operation Scheme (PIC/S), which has 52 member participating authorities, including the FDA. The FDA has been involved with developing a PIC/S training academy to train inspectors around the world on best practices in GMP assessments. The goal is more harmonization in inspections.

NIPP

Cruse gave an overview of the FDA's New Inspection Protocol Project (NIPP) [5], which embodies the desire for a better paradigm for the state of quality and compliance with cGMP. NIPP has already been implemented for sterile preapproval and surveillance, which were selected as the first area of focus due to perceived high risk.

The goal of NIPP is to modernize drug inspections by collecting and analyzing data in real time to give the FDA better information on the state of quality in drug manufacturing facilities and help in regulatory and application decisions. It supports consistent and comprehensive coverage of critical areas, uses a more structured

Regulatory Challenges: A View from Industry


Christine Moore

Christine Moore, PhD, Global Head and Executive Director, GRACS CMC Policy, Merck & Co., Inc., and session leader for the first plenary, gave a presentation during that session entitled "Innovative Technology Development and Regulatory Challenge." It included observations from the industry point of view about interactions with regulatory agencies as industry aspires to introduce new technologies.

"We are in a time of unprecedented change," Moore said. Changes include cell and gene therapy, with even small molecule products looking different and more complex, moving into drug-device combo products, continuous manufacturing, new equipment, and new ways of working. Digital technology such as artificial intelligence (AI) is also accelerating. New regulatory approaches, including ICH Q12 (published on the day of Moore's presentation), are also having an impact. As the industry shifts to produce and distribute more specialized, smaller volume products, including highly complex products like gene therapy, drug-device combinations, and antibody drug conjugates, companies face shorter timelines and are trying to do more with limited resources. This situation raises the question, "How can we work smarter, not harder? New technologies and approaches can help us do it!"

New tools can help pharmaceutical manufacturers move ahead. Flexible manufacturing facilities are one approach, and many companies are starting to make the move toward flexible and agile capacities, ranges of modalities and batches, real-time release testing, short lead-time supply chains, and a focus on variable costs. Pods and modular systems provide maximum flexibility, as they can be moved, and can be scaled for increased capacity. Whereas pods are part of host facilities today, they may be able to be stand alone in the future.

Moving from scaling up to scaling out is important. A modular system with added equipment in the same facility or pod can keep scale the same with multiple units. Continuous manufacturing offers new ways to increase the production rate by running equipment for longer times. It also offers other advantages, including the opportunity for flexible batch sizes and decreased cycle times, fast turnarounds, predictable supply, high process reliability and robustness, decreased potential for quality-related drug shortages, more potential for controlling variability, and potential benefits from mixing and hold times.

Merck is taking steps toward smaller and more flexible operations with a facility that is much smaller than traditional facilities. Such initiatives could pave the way to creating small, flexible, replicable multiple-product facilities; this level of flexibility may be especially welcome with new product launches.

Merck is invested in process analytical technology (PAT) and advanced process control in analytics, which offer many advantages, such as improved data for decision-making, early fault detection, and fewer manual interventions—all of which lead to more robust processes. These investments will help ensure product quality and more reliable production, reduce deviations, and hopefully lower the cost of goods. "This benefits industry *and* patients," Moore noted.

She listed some "what-if" scenarios that are moving closer to reality as technology offers new options, including:

- Manufacturing facilities that could be placed onto trucks and mobilized
- Medicines that could be made at a pharmacy or in the home
- Manufacturing processes that use AI to control themselves (similar to self-driving cars)

To succeed, she pointed out, these innovations will depend on regulatory requirements that are adapted to accommodate the technological changes. For example, regulations for mobile operations would need to recognize that some facilities don't have street addresses.

Moore advocated for partnering with regulators in initiatives like those discussed by the FDA and also with the EMA PAT team, Japan's PMDA Innovative Manufacturing Technology Working Group, and the UK MHRA Innovation Office. The new ICH Q12, and Q13, Q2 (R2), and Q14 in development have the potential to support new technologies.

"Regulators want new technologies and are encouraging us to use them, but new technologies are not going to happen by themselves. Proactive engagement is needed. Regulators need the use cases, and 'what-ifs' in real situations. That will spur change in regulations. We can't be afraid in industry to do things—we need to partner with regulators to move forward."

Panel members for the final plenary session (left to right): CDR Tara Gooen Bizjak, David Churchward, Jaap Venema, and Alonza Cruse.

One challenge to harmonization is that it is resource intensive. Other challenges include time, priority misalignment, technical and regulatory hurdles, and revision hesitance.

and consistent electronic format, and provides up-to-date technical information and resources for investigators.

The initiative will provide more quality, streamlined inspection reports and increase the quality focus of assessments to highlight what facilities are doing well, Cruse said. This is a departure from how inspectors are trained, which is to identify what is not going well, what is missing, or deviations.

NIPP will expand to other dosage forms, Cruse said. Protocols are under development are oral nonsterile dosage and transdermal products, creams, lotions, and active pharmaceutical ingredients (APIs). Some of these protocols may be rolled out in 2020 as pilots.

PHARMACOPEIAL COLLABORATION AND HARMONIZATION

Jaap Venema, PhD, Executive Vice President and Chief Science Officer, USP, presented on "Pharmacopeial Collaboration and Harmonization from the USP Perspective."

He provided background on USP, whose mission is to improve global health through public standards and related programs to help ensure quality, safety, and benefit of foods and other products. Public standards have value for many reasons, Venema explained. They provide a scientific basis for regulatory review, manufacturing, and enforcement decisions; they contribute to research and development, fostering innovation; they ensure a consistent approach to quality for innovator and generic products; they provide a basis for assessing the quality of drug products in commerce; and they help with monitoring for counterfeit and substandard products and quality of imported drug products.

USP works in collaboration with ICH, the World Health Organization (WHO), the FDA, other national regulatory authorities, industry stakeholders, and expert volunteers toward harmonization of global pharmacopeias. Effective pharmacopeial collaboration is valuable because it promotes access to quality medicines by leveraging global expertise; increases the value of public quality standards; facilitates global access to state-of-the-industry technology; prioritizes balancing current paradigms and future trends; and enables global pharmaceutical trade.

The USP Adopt Framework grants the rights to copy and adapt USP standards into other pharmacopeias. USP has agreements with multiple countries. Another area for collaboration is the Pharmacopeial Discussion Group (PDG) among Europe, Japanese, and US pharmacopoeias and WHO (as an observer). The focus is on harmonizing general chapters and excipient monographs, and PDG is making steady progress through retrospective harmonization: 45 excipient monographs and 21 general chapters have been completed. PDG can also help resolve issues with standards that have been stalled or are not being leveraged effectively.

Going forward, PDG aims to be more strategic and efficient and seeks to remain relevant in the globalized environment. Other goals include engagement with other pharmacopeias and regulators outside the US, EU, and Japan, as well as with ICH, and supporting and adapting to regulatory reforms.

According to Venema, one challenge to harmonization is that it is resource intensive. Other challenges include time (harmonization is a long process), priority misalignment, technical and regulatory hurdles, and revision hesitance.

PANEL DISCUSSION

Cruse and Venema were joined for the panel discussion by David Churchward, Deputy Unit Manager, Inspectorate Strategy and Innovation, MHRA, and CDR Tara Gooen Bizjak, Senior Science Policy Advisor, Office of Policy for Pharmaceutical Quality, CDER, FDA. The following are highlights from the questions and answers.

Has the mutual recognition agreement between US and EU been effective in reducing duplication of GMP inspections?

Cruse said the program has been effective; he noted that through March 2019, 173 MRA inspections were classified by the FDA, and many more were after that time, but he did not have data on the total nor the number of reports the FDA sent to the EU.

Churchward said that in the 22 months from November 2017, when the agreement came into force, until September 2019, European inspectors performed 75% fewer inspections in the US. That is a significant number, he said.

Are there "learnings" from the EU-US MRA on inspections that we can draw on and use in other similar situations?

Churchward said they are learning what to replicate for the future. One key lesson from the MRA work is being aware that mutual recognition is about equivalence, not about being exactly the same, he noted, stressing that this is an important point. "We can take that forward into other harmonization and convergence work."

With more than 20 different GMPs in the world for drug products, could ICH Q7 GMP for APIs be used as a model to create one single GMP for drug products?

Cruse noted this was a difficult question to answer. Churchward reiterated his point about equivalency being the goal and stated that, in many respects, international harmonization of GMP through the 52 authorities in PIC/S has brought the industry very close to global GMP.

Bizjak saw the question as being about using that particular model and noted that there are multiple opportunities to work toward harmonization. She added that much work already has been done. "Q7 guidance is a very powerful approach and is globally recognized, so it is possible!"

What can we do on the pharmacopeial side on harmonization/convergence, and how do we ensure our Chinese colleagues are on board?

Venema noted that he discussed harmonization and convergence in his presentation. As for China, he said he does not have an answer. However, "we have to collectively continue to build capabilities," and participation from China is welcome. He noted that USP has a fairly strong bilateral relationship with Chinese pharmacopoeia.

With quality metrics and advancing pharma quality, now FDA has a whole new source of data from MRA inspections. Has this increased the amount of surveillance database knowledge and changed the risk paradigm in other inspections?

One topic that has come up in primary team assessments of EU member states is harmonizing the format and content of reports, which would be very valuable, Bizjak said. The FDA has been working on that in its NIPP reports, and she said she has seen the benefit in setup and the ability to pull information. "Seeing that, potentially aligning reports coming in and being reviewed by ORA with the format of our reports would be very valuable to the goal of looking at and using data in a more standardized, powerful way."

Churchward added, "We are not inspecting as much in the US, so we can redirect resources." Reliance rather than recognition principles are in PIC/S, so information can be used from other PIC/S authorities to defer inspections, or there may not be a need to return to confirm if another authority will do so.

Cruse concluded, "it's an evolving area. We're in very early stages."

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A GAMP® APPROACH
to Robotic Process Automation

By Siôn Wyn and James Canterbury

This article introduces the concept of robotic process automation (RPA) and discusses how the technology may be used within a GAMP® framework to support both non-GxP and GxP processes.

We focus on deterministic RPA and do not discuss related but significantly different approaches, such as artificial intelligence (AI), machine learning (ML), or cognitive automation (CA). It is, however, the intent of the GAMP® Special Interest Group (SIG) to continue to actively consider these topics and how these approaches may be applied together [1–3]. The approach described here is consistent with GAMP® 5 and has undergone GAMP® subject matter expert (SME) review.

DEFINITIONS

RPA is a technology application that allows the configuration of computer software (a robot or "bot") to capture and interpret data from existing applications for processing transactions, manipulating data, triggering responses, and communicating with other computerized systems [1, 4, 5].

RPA technology uses software bots to mimic the activities of human workers. RPA simulates how a human user would use an application's graphical user interfaces (GUIs) to perform tasks, which the bot performs by automatically executing those tasks directly in the GUI without human intervention [2, 5, 6]. This may be likened to recording an action and then programming the bot to replay it.

RPA bots can log into applications, extract data, enter data, complete tasks, and log out. RPA technologies can be divided into three types: probots, knowbots, and chatbots [7]. This article focuses on probots—bots that follow simple, repeatable rules to process data. Other types of bots are knowbots, which search the internet to gather specific information, and chatbots, which respond to human input or queries in real time.

RPA software is not always considered part of an organization's traditional IT systems architecture. Rather, it is sometimes regarded as sitting on top of that architecture, with RPA software implementation and operation being possible without changing the existing systems [1, 2, 5].

It takes little or no previous experience to program bots, and separate application bots may not change the underlying systems; however, RPA bots can influence the business process and related data. Therefore, their use should be carefully planned and controlled.

COMPONENTS

RPA technology consists of the following main components: the underlying package or product, the individual bots, and the automation or script (see Figure 1).

Underlying Package or Product

The underlying package or product is classified as GAMP® Category 1 software. Examples of platforms or products characterized as RPA include, but are not limited to, Automation Anywhere, Blue Prism, EdgeVerve, HelpSystems, UiPath, Workfusion, Kofax, NICE, PegaWorld, and Kryon. This list of example platforms and products is included for convenience only and should not be regarded as complete or definitive.

Individual Bots

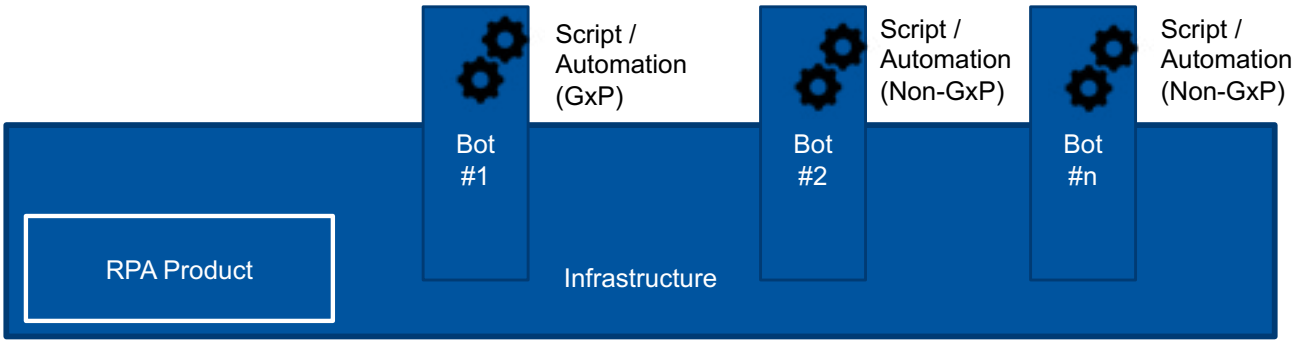
The bots will be set up (or qualified) as general infrastructure components that are ready to use with some general account, access control, and security settings. They can then be instructed to perform specific business processes (GxP or non-GxP) as required by means of specific automations or scripts.

The individual bots are GAMP® Category 1 software components. Such bots—like people—can be regarded as a multiskilled workforce, ready to be instructed in a specific process by means of a defined automation or script. Multiple bots can run any individual automation, and any bot can run multiple automations. This is analogous to multiple qualified human operators being able to follow a specific standard operating procedure (SOP), and a qualified human operator being able to follow multiple SOPs.

Automation or Script

The automation or script can be considered a stand-alone application and should have an appropriately managed life cycle. Business processes and rules need to be defined, and the bot needs to be configured to perform specific activities and meet the business rules, following the defined process. A controlled life cycle is needed for these scripts or automations, starting with planning and progressing through specification, verification, and release into the operational environment.

Figure 1: Components of RPA technology.



The automations and scripts are classified as GAMP® Category 5 components (equivalent to small stand-alone custom applications). The deliberate choice to include them in Category 5 reinforces the need for a controlled life cycle for these scripts or automations from planning through specification, verification, and release into the operational environment. The effort involved in the specification, verification, and related documentation should be scaled according to risk, complexity, and novelty following normal GAMP® principles.

Another valid approach may be to regard the scripts or automations as analogous to individual batch instructions or workflows (having their own controlled life cycles and validation), similar to those running on an underlying electronic batch record or manufacturing execution system (MES) platform. Again, the underlying life-cycle activities and controls would be the same (i.e., specification, verification, release management, and subsequent change management).

TYPICAL APPLICATIONS AND PREREQUISITES

RPA is best suited for stable processes that use structured data and have explicit and well-documented business rules, with high transaction volumes and typically with a "single correct answer" [1, 2, 5, 6].

RPA is often applied to automate "swivel chair" tasks—tasks that employees perform by swiveling (often literally) between applications or computers to manually extract information from one application, check or validate it, and then enter it in another application [5]. RPA applications may include automating time-consuming processes, such as when users need to log in to third-party sites to download items on a regular basis.

Typical uses of an RPA process include the following:

- Bots are set up as email "listeners" to kick off other processes. For example, when given the email trigger, "Here is the link to the file you requested," the bot logs into the third-party system and downloads the file. When it is downloaded, the bot parses and integrates the data into an existing data set.
- If a requester fills out an email form that requires more than just simple field validation, a bot can perform the initial verification checks—such as "Does this request already exist?"—and swiftly provide an initial reply to the requester.

Prerequisites for successful application of deterministic RPA include stable processes, clean data, and established and documented business rules that are sufficiently well defined and detailed enough for automation [1, 2, 5, 6]. It is good practice to redesign the process for automation, instead of simply automating the "as is" human process, which may involve logging on and off many times or not batching activities for efficiency.

RPA may be appropriate when the underlying source system is not a good fit for its purpose. Alternatively, RPA may be desirable when a change to the source system is especially complicated or difficult, or when two systems are difficult to integrate. Choosing to use RPA may also be a purely business decision, which may have multiple underlying reasons, including budget constraints.

Where RPA is introduced to address an underlying functional or integration issue, a longer-term strategy may be required to address the problem. It is often good practice at the start of RPA projects to develop a longer-term (e.g., three- to five-year) plan whereby the RPA functionality is replaced by permanent changes to the underlying systems or further redesign of the business process.

BENEFITS AND RISKS

For rule-based deterministic processes that are digital and repetitive, properly implemented RPA can improve quality and reduce

Properly implemented RPA can improve quality and reduce business risks and errors.

business risks and errors, offering opportunities for high availability, consistency, productivity, accuracy, and reliability [1, 2, 5, 8]. RPA also offers an opportunity to lower compliance and quality risks associated with nonintegrated systems in different functional areas (i.e., "siloes"), which may currently depend on manual interactions, manual transcriptions, or work-arounds to share data within the same or related processes [9]. RPA can also provide comprehensive time-stamped activity logs, which may be used for process analysis [8].

With RPA, test cases are easier to define and perform due to clear rules and objective processes (typically with one correct or expected outcome). RPA is a good candidate for the application of automated testing, especially regression testing, and RPA tools have technical similarities to GUI testing tools. RPA also lends itself to an approach of establishing a library of verified building blocks—tested once and used many times.

RPA interacts with systems through existing, defined user transactions and uses predefined logic, avoiding the need for more complex and potentially invasive system integration approaches such as application programming interface coding and new custom interfaces, which would require more extensive testing [1, 4, 5]. This also allows the continued leveraging of the definition, specification, design, and testing of existing system requirements (e.g., system functionality and features related to error prevention, data integrity, security, and access control). Requirements for regression testing when scripts are modified may therefore be substantially lower, as the previous verification of existing systems is still valid. Verification can be tightly focused on the correct definition of the business rules, as well as the verification of the script or automation against business rules within the defined process. Data structures in existing systems are unchanged.

However, as discussed later in this article, the use of RPA may introduce new challenges and risks associated with security and access control in the operational environment [1]. These risks require specific assessment, application of appropriate security and access controls, and verification of such controls. This is likely to be a primary element of risk management for RPA.

Error and exception handling are a major design consideration. In such cases, enough information should be provided to the appropriate person so that timely action can be taken, which will typically require establishing local or centralized monitoring mechanisms. Errors and exceptions should be addressed and should not cause the process to hang or terminate, unless this is a process design decision.

Error and exception handling should be rigorously tested. This reflects the EudraLex Volume 4 Annex 11 requirement that "particularly, system (process) parameter limits, data limits and error handling should be considered" during testing [10].

The overall risk-benefit balance is favorable given the application of an appropriate life-cycle approach and operational controls.

AUTOMATION/SCRIPT LIFE CYCLE

Like any more traditional custom application, RPA requires the normal life-cycle steps and activities:

- Definition of intended use, including business and quality objectives
- Life-cycle and quality planning
- Definition of the "to be" process, including identification of data and definition of data flow
- Definition of business rules
- Definition of detailed logic and other requirements
- Configuration, scripting, or training (or whatever terminology is preferred)
- Verification
- Life-cycle and quality reporting
- Controlled deployment
- Application of operational controls (see next section), including change management

Typically, scripting, configuration, or training and subsequent verification are performed in development environments substantially equivalent to the production environments.

An iterative and incremental (Agile) approach may likely be the most appropriate option. The most practical and advantageous strategy may be to initially and quickly apply the approach to the cases where most business benefit is achievable, and to automate the most common paths first, while putting a framework in place that allows both refinement of existing rules and application to less-common paths as time and resources allow.

Such an iterative and incremental approach requires that the appropriate technical and project management skills and experience are available. It also depends on necessary input from line-of-business owners and business process SMEs, as well as from quality assurance for applications supporting critical GxP processes.

RPA scripting/automation tools are typically designed to be used by individuals who do not have extensive programming skills and experience (or, at least, that is what the marketing promises). However, the appropriate involvement of IT and relevant technical SMEs is necessary to ensure, for instance, that purchased software is safe, appropriate, and technically compatible with existing

infrastructure; data security and access control policies are applied; suitable backup or equivalent arrangements are in place; and bots operate on a reliable and managed infrastructure [1].

This reflects the EudraLex Volume 4 Annex 11 requirement (11.2 Personnel) that "there should be close cooperation between all relevant personnel such as Process Owner, System Owner, Qualified Persons and IT" [10].

OPERATIONAL ASPECTS

Key operational aspects to consider include access and security management and change management [1]. For access management, existing policies should be followed but suitably adapted to the needs of a substantially different situation. For example, it would be inappropriate in most cases for bots to use existing human user IDs and passwords, and rules and policies for the following would need to be adjusted:

- Who sets passwords?
- How are they updated?
- How are password aging policies applied?
- How are password compromise policies applied?
- To what extent would sharing accounts and passwords be a problem?

Security and compliance rules must be adapted, and many behavioral risks and controls may no longer be relevant. Examples are rules related to auto logoff and auto screen lock. The practical application of the principles of separation of duties should be considered.

Data integrity and security risks should be assessed and managed. Concerns may include the security of permanent or temporary data storage, including vulnerability to human users; human access to desktops; and the possibility that a user could take over control from a bot. If the bots must be manually started, only authorized individuals should be able to do so. Both physical and logical access controls should be considered.

Auditability of data changes may be a factor to review and adjust. To what extent is a log entry required if a bot modifies or deletes a GxP record? The answer to this question would have to be very specific, well defined, and validated as conforming to the relevant business rules and policies.

Change management must cover cases when business rules or objectives change, situations in which the functionality or behavior of the associated systems changes, alterations in data models or data structures, and any changes to the underlying IT environment. Some products offer a centralized change and release management and distribution model, which may assist in managing all types of changes.

When considering potential RPA applications, it can be interesting and fruitful to consider analogies to human resources (HR) challenges. For example, HR-like plans must be made for bot availability and start-up, task completion, exceptions, monitoring (especially to deal with errors and exceptions), performance review, and retraining [1].

CONCLUSION

If applied to suitable processes and use cases within a GAMP® framework of quality risk management with appropriate project and operational controls, RPA can offer business and quality benefits and the overall risk-benefit balance may be favorable. For this reason, the GAMP® SIG continues to investigate how RPA and related technologies, such as AI, ML, and CA, may help the pharma industry achieve its business goals and promote patient safety and public health.

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About the authors

Siôn Wyn, Director, Conformity Ltd., is an acknowledged expert in computer system validation and compliance. He assisted the US FDA as a consultant with its reexamination of 21 CFR Part 11 and was a member of the core team that produced the FDA Guidance on 21 CFR Part 11 Scope and Application. He was the Technical Content Expert for the FDA's ORA Virtual University online training modules on computerized systems validation and compliance. He received the FDA Group Recognition Award for work on Part 11. Siôn is the Editor of ISPE's *GAMP®5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems*, Co-lead of the ISPE *GAMP® Guide: Record and Data Integrity*, and a member of the ISPE GAMP® Global Steering Committee and GAMP® Editorial Board. He received the 2006 ISPE Professional Achievement Award, which honors an ISPE member who has made a significant contribution to the pharmaceutical industry, and he received the ISPE UK Fellow Award in 2016. Siôn has been an ISPE member since 1995.

James Canterbury is a Principal in EY's Risk Advisory practice and a leader in EY's global blockchain team. He helps his clients understand new technologies and how they might be applied to solve real-world problems. Specifically for blockchain, he focuses on solutions to capitalize on the benefits of distributed networks that are efficient, transparent, and trusted. James has 15 years of experience helping life sciences companies find innovative answers to the challenges created by operating in a highly regulated industry. Before blockchain, he primarily managed projects that spanned from interpreting FDA regulations to privacy and security to financial controls. James holds a BS in industrial engineering from Penn State University and is a Certified Information Systems Auditor. He currently sits on the board of the New Jersey Chapter of ISPE, is the Co-chair for the Global GAMP® Steering Committee, and leads the GAMP® Blockchain Special Interest Group. He has been an ISPE member since 2015.

WEARABLE DEVICES AND BIOMETRICS

to Improve Efficiency in GxP Operations

By Davide Smaldone

This is the second in an ongoing series of articles about Pharma 4.0™.

As the old saying goes, "Time is money." In today's industrialized world, this adage is profoundly true. Manufacturers can no longer afford to overlook operational excellence. A new production philosophy called "Lean manufacturing" has been developed to save as much time as possible during manufacturing processes. In some industries, such as the automotive sector, Lean has almost been perfected. However, in pharma, we are still seeking perfection. Despite recent efforts, there is still plenty of room for improvement.

In a highly regulated environment, *attributability* is a core principle that must be constantly respected. It is so important that it is included in the ALCOA+ framework, which identifies key characteristics for data: attributability, legibility, contemporaneousness, originality, accuracy, availability, endurance, consistency, and completeness. Data integrity demands that GxP-relevant data have all these characteristics. Wearable and biometric technologies can help ensure attributability in an efficient and compliant way, while also improving other aspects of production.

CONVENTIONAL METHODS TO AUTHENTICATE OPERATOR IDENTITY

To ensure that a specific operation is uniquely linked to an individual, the individual must authenticate their identity when performing a GxP-relevant activity. For example, operators in production are asked to authenticate their identity dozens of times throughout a single shift. In some cases, an old-fashioned pen-and-paper signature is required; however, a specific user typically provides an e-signature by entering their username and password. While this operation is simple in normal life, it becomes cumbersome in a production setting where the worker is wearing gloves and other protective gear and typing on a special washable keyboard.

WEARABLE AND BIOMETRIC ALTERNATIVES

In recent years, companies have started looking closely at alternative ways to effectively facilitate the authentication process without compromising data integrity. Initial solutions allowing users to scan their badge and enter a code in the system were explored and sometimes implemented. However, this approach did not solve the problem for operators working in controlled environments. When ID cards are used, there is no safe way to ensure that they are used properly.

In contrast, *wearables*, an Industry 4.0–enabling technology, have provided an effective solution that eliminates the need for e-signatures and helps operators work better and faster. Devices such as smart watches, bracelets, and wristbands with contactless connectivity can authenticate users with a simple swipe. Such devices are equipped with a sensor that can detect when the watch or band is being worn.

Authentication using a wearable device can take place in different ways. Generally, users are asked to authenticate themselves at the beginning of each shift. Logging in can be performed in a traditional way by inputting a username and password at an enrollment station, which pairs the operator with a specific device (if one is not issued personally to each employee). Alternatively, in solutions such as the one in the solution proposed by Nymi, the operator can log in by pressing their index finger on the wristband. After authentication, e-signatures can be made in a fully compliant way through the swipe of an arm close to a specific reader. If the operator removes the device, it automatically detects that it is no longer being worn and logs off the user. The user cannot perform any other signatures until the band or watch is worn correctly and the user has logged in again.

Another way of authenticating users is through biometric data, such as fingerprints. Whenever the user must provide an e-signature, they touch the wearable device with their index finger. The device reads the operator's fingerprint and automatically signs with their credentials.

SAVING TIME AND IMPROVING SAFETY

Entering a signature on a keyboard could take 10 to 15 seconds, whereas signing via a simple gesture takes just a couple of seconds. This means a significant saving of up to 20 minutes for every 100 signatures, which is especially relevant for operators working in production phases that are classified as "e-signature intensive" (e.g., weighing and dispensing). For an operator who is called to sign off 50 times per shift, use of wearables could lead to a potential total saving of 40 hours per year (assuming one shift per day for 220 days per year). That is a significant amount of time, which could be used to carry out more relevant tasks or reduce operator workload.

In addition to authentication, smart watches can also be used for other purposes. For example, they can notify a specific operator or shift supervisor about a problem that requires attention, or dispatch a ticket to a team of maintenance operators. Once the maintenance operator receives the ticket notification, they can take charge of the issue simply by swiping on the display. The use of such devices could also improve the company's health and safety profile by detecting "man down" situations and quickly and effectively notifying operators working in an area where a safety issue has occurred.

CONCLUSION

Wearable and biometric technology in the pharma industry is moving forward. Vendors such as APPforGood and Nymi have started offering solutions similar to the ones described in this article, and there are proven and interesting use cases that suggest the devices can be affordable and demonstrate a positive return on investment.

> Signing via a simple gesture takes just a couple of seconds.

About the author

Davide Smaldone is Corporate IT Demand Manager at Menarini Group. He holds a master's degree in management engineering and has more than 10 years of experience in complex IT transformation projects with a specific focus on the pharmaceutical industry. He supports Menarini business and IT in delivering complex system-driven solutions, manages the IT Project Portfolio for all GxP relevant areas, and is responsible for Industry 4.0–related initiatives. Davide is an Executive MBA candidate at SDA Boccorn School of Management. He is part of the ISPE Pharma 4.0™ Advisory Board and Special Interest Group. Davide has been an ISPE member since 2015.

MISSION-DRIVEN LEADERSHIP

By Paul Cumbo

Pam Cheng is Executive Vice President, Global Operations & Information Technology, at AstraZeneca, a United Kingdom–headquartered pharmaceutical company with more than 60,000 employees. In this role, she combines her expertise as an engineer with business savvy and seeks opportunities to lead her company and her industry forward in innovative ways.

The path that brought Cheng to this leadership role is a vocational journey inspired by a comprehensive skill set coupled with a genuine love of learning. Among several other influences, Cheng credits her father for encouraging her to pursue a scientific vocation. "He wanted me in STEM fields," she explained, and he used reverse psychology to convince her. "To challenge me, he said, 'One thing I do know is that you won't pick a technical major like engineering, because girls can't make it.'" Cheng described how, years later, she'd say to her father "You know, Dad, it's a good thing I really do like it. I don't know how I would have forgiven you if I hadn't."

Before joining the AstraZeneca team in 2015, Cheng served as President of MSD (Merck) China for four years. Prior to that, she held other leadership roles in global manufacturing and supply chain at Merck/MSD. Earlier in her career, Cheng worked in engineering and project management positions at Universal Oil Products, Union Carbide Corporation, and GAF Chemicals.

FROM ENGINEERING TO BUSINESS MANAGEMENT

Cheng has undergraduate and master's degrees in chemical engineering and an MBA. "I knew I wanted to further my studies after my master's and working professionally. My immediate desire was to pursue my PhD in chemical engineering because I've always wanted that 'Dr.' title next to my name! But I was working in the petrochemical industry at the time and loved what I was doing, and I didn't want to disrupt my work by pursuing a PhD." After briefly considering law school, Cheng realized that an MBA was the right next step for her career.

Pam Cheng

"Business school taught me about different ways of thinking," Cheng said. "With engineering, there is often a very technical approach—how to get from point A to point B, and how to solve problems. Business school was my first exposure to genuine diversity of thought and different forms of creative problem-solving." Cheng discovered an affinity for business operations and a new level of enthusiasm for her career options. "It's a little bittersweet that I never earned that PhD, but if I had, I would have gotten into deep technical research roles, and I would have taken a completely different career path." Cheng believes that openness to these kinds of career crossroads is vital. "I often say to the younger talents that come to me for coaching, 'You just have to go and try it out. You won't know about a direction or what you can do until you take a risk and do it.'"

VOCATION AND MISSION

Cheng believes deeply in the fundamental purpose of her work, and that of the pharmaceutical industry as a whole. "There are many ways to earn a good living, but being able to make a living with a

mission is a privilege," she said. The industry "has an undeserved [negative] reputation—indisputably, it saves and improves lives."

She appreciates the tenacious work ethic and pursuit of excellence demonstrated by her industry colleagues. "This industry has taught me the importance of relentless focus and innovation, as well as what great science, technology, and committed people can do," she said. Asked about the role of leaders in this mission-driven context, she emphasized the importance of setting the stage for individuals and teams to maximize their potential. "The role of leaders within the industry is to foster an environment of inclusion and diversity, setting clear objectives and boundaries while allowing passionate and committed professionals to unleash their creativity and capabilities," she said.

INDUSTRY 4.0 CHALLENGES AND OPPORTUNITIES

The Fourth Industrial Revolution is transforming every industry, and pharmaceuticals is no exception. As a business leader, Cheng has an integral role in the ongoing process of adaptation and innovation such transformation requires. "Every company in and out of the biopharma industry is wrestling with the Fourth Industrial Revolution and digital transformation," Cheng explained.

"There is no mistaking that we are living in a digital era," she said, but the pharma industry tends to move slower than some others "because there's so much at stake. Discovering, developing, manufacturing, and supplying medicines is traditionally a lengthy, costly, and risky process."

Although Cheng understands why innovation in pharmaceuticals takes time, she is also open to questioning the traditional assumptions that contribute to the slow pace of change. "Does it have to be this way moving forward? We are seeing an unprecedented explosion of new technologies and digital innovations that can change what we do, and how we do it. This includes the way we discover, the way we develop, the way we manufacture and supply. Data generation and availability are increasing at an amazing speed." Cheng believes that people, not technology, are the key factor in Industry 4.0 endeavors. "The companies that put people at the heart of the transformation will have a higher success rate. It's 10% technology, 90% people!"

Many industry leaders are finding this to be true and are realizing that the human element is integral to innovation. In a 2019 white paper, "Leading Through the Fourth Industrial Revolution: Putting People at the Centre" (https://www.weforum.org), the World Economic Forum stated that "responsible leadership of the production workforce—now and in the future—is predicated upon a human-centric mindset."

"Digital transformation poses great challenges to people at all levels of their careers," Cheng said. "The estimated half-life of acquired skills is approximately five years. This means what we learn today, chances are will become obsolete in less than five years. How can we help ourselves? By adapting a more agile and flexible mindset, being more open to learn at every stage of our career, and staying connected."

Cheng encourages industry leaders to support their employees' development. "We must foster a culture of lifelong learning. We don't need to restrict employees by their formal job description. We should allow and encourage them to experience and learn from different areas. This way, we can unleash people's experiences and insights to solve problems and move business forward, regardless of their role."

About Industry Leaders

The Industry Leaders series profiles the lives and careers of individuals who are changing the face of the pharmaceutical industry. This profile is the latest in the ongoing series. Please see the introduction to the series, "Introducing Industry Leaders," and profiles of other leaders in January-February 2020 *Pharmaceutical Engineering*, as well as the Member of the Year profile in March-April 2020 *Pharmaceutical Engineering*.

> "This industry has taught me the importance of relentless focus and innovation, as well as what great science, technology, and committed people can do."

Cheng's desire to empower her employees has led her to leverage the notion of a "gig economy" for talents. "I was talking to someone in a particular role at AstraZeneca. He said, 'Well, this job only taps into about 20% of my knowledge and experience.' It was an 'aha' moment. I knew he loved his job, but he wanted to use that other 80% to contribute to what we do." Cheng thought about the success of companies such as Uber and wondered whether there was a way to "deploy the notion of the gig economy within the workplace" to help employees connect and go where they are needed. To achieve this goal, she began using Workplace, a Facebook platform for companies, to facilitate and encourage cross-departmental connections to solve problems.

She offered an example of the system at work. "We had a technical challenge at one of our sites," she recalled, "but we didn't have folks with the technical skills readily available. So we used the network and searched based on key skills. We built a team quickly, and it was made up of people from a range of roles in the company—people who normally wouldn't work together directly." Cheng explained the immediate and secondary benefits: "It solved a problem, and it got people out of their normal rhythms and enabled them to bring different skills to the company. That gave them real satisfaction. It gave a hint of a potential situation where people can add value beyond their job descriptions. I can also connect more experienced people and newer employees; they can benefit from each other's perspectives by working together." The challenge now, she commented, will be to scale up more broadly within the organization.

This emphasis on dynamism is central to Cheng's leadership philosophy. "People get complacent. They find their jobs and they settle in for life. Given the half-life of skills we find today, we have to help our workforce. I employ more than 18,000 people globally. Do I fire half of them when their skills become obsolete and rehire? Or do I drive a culture of lifelong learning? Of course, the latter!"

WOMEN AS LEADERS

Cheng is an advocate for expanded diversity in the pharma industry. "I'm working with some of the best and brightest in the technology and science areas, both women and men. More and more women are excelling in the technology and digital space. It is a fact that more diversity in companies brings more innovation, creativity, and business success: not only gender diversity, but diversity of thoughts, experiences, and ways of working.

"Although there are clearly more women in top technical jobs, statistics would tell us that we still have a ways to go to achieve a good balance. I'll repeat that notion of 10% technology, 90% people—and women leaders can play significant roles in driving organization transformation in thoughtful ways," she said.

Cheng is proud that women hold 45% of senior roles at AstraZeneca. "It takes conscious and thoughtful actions to support and foster female leadership," she said. "We promote based on merit, but we recognize that providing the right support, coaching, and encouragement throughout their careers is critical in developing female leadership. A balanced leadership team has direct impact on the company's performance."

KNOWLEDGE-SHARING AND ISPE

Cheng believes in the power and importance of knowledge-sharing among members of the industry, and she sees ISPE at the center of these efforts. "ISPE has always been the industry leader in connecting pharma knowledge, focusing on all aspects of manufacturing and supply chain," she said. It was key to her own career development as well. "I've found that ISPE is where the knowledge resides for me as I've matured in engineering. It facilitates collaboration among the companies, sharing of good practices, and connecting on key regulatory and technical insights. Such collaboration and sharing are key to the success of the industry. When it comes to women in engineering, ISPE's Women in Pharma® promotes growth at all levels."

EXCITEMENT FOR THE FUTURE

Cheng's energy and enthusiasm for her work are hard to miss as she speaks about the industry's future. "We are faced with unprecedented opportunities to up our entire value chain, from discovery to supply. Imagine enabling new medicines for unmet medical needs in one-half, or even one-third, of the time it takes today. Imagine building the factory of the future enabled by digital technology. Imagine the ability to not just 'treat' patients but also make a difference in the entire patient journey from awareness and diagnostics to treatment and to wellness."

"In general, I'm excited about what data and digital technology can do, but like anything else, we have to be thoughtful," she emphasized. Her knowledge, skills, and experience give her a balanced disposition—an essential quality for key players in such a high-stakes industry.

About the Author

Paul J. Cumbo, MS, MLitt, a veteran high school teacher and administrator, is a freelance writer, editor, and communications consultant serving a variety of industries. He has collaborated with some of the world's most well-known Fortune 500 manufacturers, consulting firms, and global nonprofits, including the World Economic Forum, on projects ranging from internal documents to major white papers and other publications. His work for *Pharmaceutical Engineering* began with the July–August 2018 cover story on the Fourth Industrial Revolution featuring Enno de Boer of McKinsey & Company. He is a Principal and Cofounder of the Camino Institute, which offers service-oriented travel and retreat experiences for families and organizations.

BENEFITING FROM GROWTH OPPORTUNITIES:

ISPE Brazil Affiliate

By Mike McGrath

Brazil's regulatory authority is working hard to make the nation a larger player in the global pharmaceutical market, and these efforts appear to be working: the life sciences industry has expanded in recent years, and market projections are positive. These ongoing developments represent opportunities for the ISPE Brazil Affiliate as it undergoes its own transformation.

Members of the Brazil Affiliate gather in February 2020 for an Affiliate board and committees meeting.

A FLOURISHING MARKET

Brazil is the largest country in South America and, with a population of 212 million, it is the sixth most populous country in the world. According to a 2019 report from the Brazilian pharma industry trade group Interfarma, the Brazilian pharmaceutical market grew 11% in 2018, reaching R$90 billion (US$20.12 billion). Interfarma projects that the market will continue to grow, becoming the fifth largest in the world in the next few years [1].

This growth is being supported through the work of ANVISA, Brazil's national health surveillance agency, which has been implementing new regulations and guidelines intended to align the Brazilian pharma industry with international standards. In late 2016, ANVISA was accepted as a new member agency of ICH. ANVISA has also applied to join the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

"When ANVISA aligned with ICH and PIC/S, they released new regulations," explained ISPE Brazil Affiliate president Mario Brenga Giampietro. "This is bringing a lot of opportunities to ISPE in Brazil. ISPE is always ahead of new technologies, and our guidelines will help companies to become compliant with these regulations."

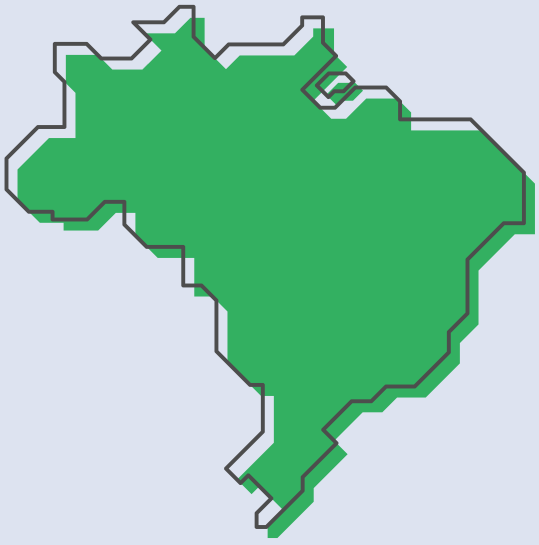
AFFILIATE GROWTH

To respond to these opportunities, the Brazil Affiliate is transforming. The Affiliate increased its number of Communities of Practice (CoPs) from six in 2018 to 17 in 2019. "We found that the best way to allow people to discuss things, share knowledge, and improve networking is through these committees," said Giampietro. "In October 2018, we had a big meeting and presented these ideas to people in ISPE who are deeply involved in the pharmaceutical market. Then we invited them to help start or be part of these CoPs."

Founded in 1999, the ISPE Brazil Affiliate is based in the country's largest city, São Paulo, which is also home to a cluster of pharmaceutical companies. In the last year, the Affiliate has seen its membership increase by over 38% to 163 members, including representatives from other sectors of the life sciences such as veterinary sciences, cosmetics, and medical devices. "Our creation of the CoPs has helped us gain more volunteers and associates here in Brazil," Giampietro said.

As the membership has grown, the Affiliate has expanded the number of events it hosts. In 2019, the Affiliate held 42 events—four more than in 2018, with an impressive 38% increase in event

Quick Facts about the Brazil Affiliate



Founded: 1999

Region: South America

Membership: 163

Executive Board

- **President:** Mario Brenga Giampietro, Nordika Consulting
- **Vice President:** Ricardo Vicente Miranda, RM Consulting
- **Secretary:** André Keity Goto, Astrazeneca do Brasil
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Committee Leaders

- **Project Management:** Flavio Lisboa, Nordika Consulting
- **Good Engineering Practices:** Flavio Lisboa, Nordika Consulting
- **Sterile Processes:** Renato Rahal, ABH
- **Containment:** Fabiana Bonvini, IMA Brasil
- **Sustainability:** Silmas Pareico, Nordika Consulting
- **HVAC:** João Carlos Corrêa da Silva, Ergo Engenharia
- **GAMP®:** Cristiano Behringer Ferrari, Nordika Consulting
- **Risk Mapp:** Marcos Pereira, Janssen Cilag
- **Cold Chain:** Ricardo Vincente Miranda, RM Consulting
- **Commissioning & Qualification:** Ana Marie Kaneto, AM Kaneto—Tecnologia em Treinamento
- **Serialization (track and trace):** Paulo Machado, Markem-Imaje
- **Calibration:** Ivan Canever, Inca Consultoria
- **Medical Device and Application Validation:** Leader to be determined (TBD)
- **Critical Utilities:** Marcio Zanatta, Telstar/Azbil
- **Pharma 4.0™:** Cristiano Behringer Ferrari, Nordika Consulting
- **Women in Pharma®:** Liana Montemor, Polar Técnica
- **Supply Chain and Logistics:** Carlos Eduardo Corrêa Coimbra, CEC Consulting
- **Regulatory:** Kátia Anunciata dos Santos, Consultora
- **Biotechnology:** Leader TBD
- **Quality Control:** Leader TBD
- **Smart Supply Chain:** Leader TBD
- **Marketing:** Leader TBD
- **OSD:** Leader TBD
- **API:** Leader TBD

attendance. Almost all the events were held in or near São Paulo, and all were on technical subjects, said Giampietro.

STRENGTHENING INTERNATIONAL RELATIONSHIPS

Giampietro hopes to improve the Brazil Affiliate's relationships with other ISPE Chapters and Affiliates around the world. "ISPE's global network has been very helpful for us," he said. "The relationship between the Brazil Affiliate and ISPE's global headquarters is very good, very strong. But we want to strengthen the relationships linking our local committees with global CoPs, such as those focused on GAMP®. This is very important, but it's a current weak point."

The Brazil Affiliate also plans to reach out more to other ISPE Affiliates in the region, particularly Argentina and Mexico. "The ISPE Mexico Affiliate is new, and we'd like to work with them and Argentina on regulatory initiatives within Latin America." In addition, the Affiliate intends to increase its role within the North America and South America Affiliates and Chapters (NASAC) group.

CONCLUSION

As he looks forward, Giampietro, who has been an ISPE member since 2006 and is entering the second year of his two-year Affiliate presidency, is excited by the Brazil Affiliate's positive relationship with ANVISA. "The new ANVISA regulatory movements are very important, and ISPE Brazil will be there to help them whenever they need it."

He emphasized that the Affiliate's future success will depend on the commitment of its members. "Our main challenge is for people to find the time to volunteer in ISPE initiatives," he said. "Some companies allow people to attend ISPE events during business hours, but it takes volunteers time to develop these initiatives—and that has an impact on their private lives. We have the people who will help, but it's difficult to attend meetings, answer emails, and prepare articles or presentations. To prepare a good one-hour presentation, you may need 20 hours or more." Recent expansion in the Affiliate suggests that pharma professionals in Brazil are up to this challenge.

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About the author

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ISPE BRIEFS

Pharmaceutical Engineering® Online Exclusives: Another Content Resource

By Susan Sandler

Pharmaceutical Engineering has launched another new section on the *Pharmaceutical Engineering* Online site: Online Exclusives. PE Online Exclusives are articles published exclusively on the PE website (https://ispe.org/pharmaceutical-engineering). This new feature expands the content available to PE readers and offers another way for ISPE to provide value to our members.

Online Exclusives include features, technical content, and interviews—the same types of content published in the print and online editions of *Pharmaceutical Engineering*. Online Exclusives is part of *Pharmaceutical Engineering*, just as PE Online itself is part of the magazine. Having the ability to publish new content on the web site allows ISPE to deliver more content to readers. And the schedule for this content won't be driven by the publication dates of the print magazine; Online Exclusives content will be added more frequently.

All *Pharmaceutical Engineering* content is reviewed and edited according to the same quality standards, whether published in print or online. This includes subject matter expert peer review and copyediting by technical editors. See the Author Guidelines for more information on *Pharmaceutical Engineering's* processes—they are designed to provide high-quality, relevant content to the industry.

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As with all *Pharmaceutical Engineering* content, Online Exclusives content is eligible for the Open Access pilot, which means that it may be unlocked for viewing by any visitors to the PE Online site. Content not included in the pilot is locked for viewing only by ISPE members.

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Pharmaceutical Engineering Online already features original online-only content through the popular iSpeak blog, and in White Papers and Sponsored Content that are provided by ISPE partners. None of the online-only content is published in the print *Pharmaceutical Engineering*, but it shares space on the ISPE website alongside *Pharmaceutical Engineering* content. This is part of ISPE's ongoing expansion of content for our members and the scientific and engineering community.

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About the author

Susan Sandler is the Senior Director, Editorial, for ISPE.

Looking Ahead: 2020 ISPE Annual Meeting & Expo in Philadelphia

Pharmaceutical Engineering will be at the 2020 ISPE Annual Meeting in Philadelphia, and we hope to see you there!

One scheduling change to note: Due to the US Election Day on 3 November, the traditional Tuesday Night Party will move to Monday, 2 November. Mark your calendars and check back frequently for details on Annual Meeting plenaries, sessions, and other important information at https://ispe.org/conferences/2020-annual-meeting-expo

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GOOD ENGINEERING PRACTICE
in Risk-Based Commissioning and Qualification

By Chip Bennett, PMP

Over the years, the roles and responsibilities of engineering and quality/validation personnel for commissioning and qualification (C&Q) activities have evolved. Now more than ever, C&Q approaches based on quality risk management (QRM) principles rely heavily on engineering and the application of Good Engineering Practice (GEP) to provide documentation for the qualification package.

This article explores the current industry transition of principle ownership of process manufacturing performance verification from quality/validation to engineering—a transition that empowers both engineering and quality personnel with the tools to deliver true quality by design, resulting in improved product quality, improved patient safety, and increased speed to market.

THE EVOLUTION OF QRM AS THE BASIS FOR C&Q

The ISPE *GAMP Guide* introduced the V Model in 1994 [1]. In 2001, the first edition of ISPE *Baseline Guide*, Vol. 5, *Commissioning and Qualification* (the "C&Q Guide") introduced commissioning and the use of impact assessments as a formal means to identify a system's potential impact on product quality [2]. This C&Q process became the pharmaceutical industry's standard practice, but manufacturers have rarely implemented it to its full potential with respect to efficiency or the integration of engineering and quality roles and responsibilities.

After the first edition of the C&Q Guide was published, additional resources became available. ICH Q8, Pharmaceutical Development, introduced and defined the concepts of critical quality attributes (CQAs) and critical process parameters (CPPs); ICH Q9, Quality Risk Management, provided a framework for a holistic QRM program; and ISPE published a white paper, *Risk-Based Qualification for the 21st Century,* describing the application of QRM principles to C&Q [3–5]. ASTM E2500, *Specification, Design, and Verification of Pharma/Biopharma Manufacturing Systems and Equipment*, provided guidance on how these concepts could be integrated into a science- and risk-based approach to C&Q [6], and ISPE published two additional guides—one describing the ASTM E2500 approach in detail, and one describing a transitional approach [7, 8]. These industry efforts culminated in the 2019 publication of the second edition of the C&Q Guide [9], and there are high expectations that this edition will establish QRM-based integrated C&Q as the industry-standard approach, using common terminology and methodology. (The other ISPE guides described here are no longer available.)

Engineering vs. Quality Roles in the QRM-Based C&Q Model

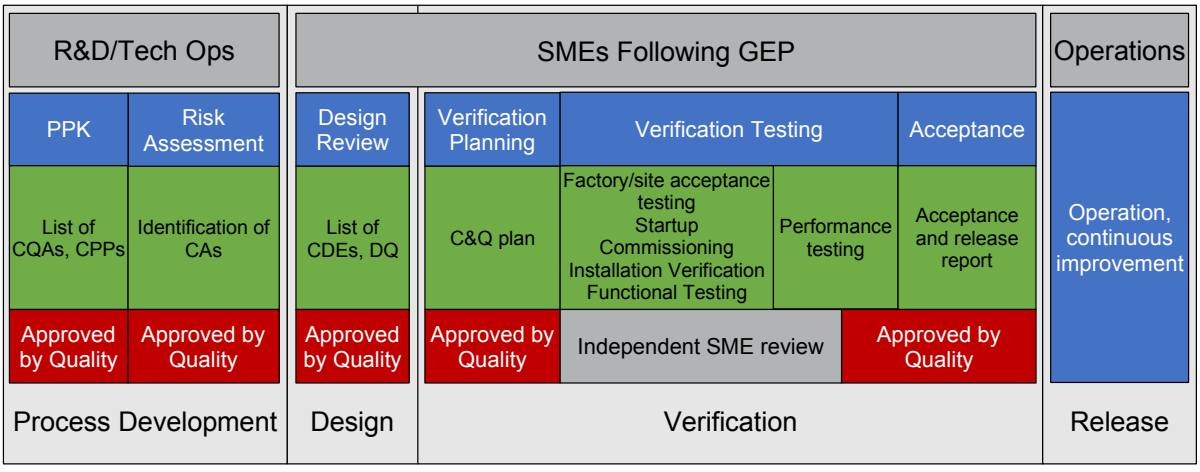
As defined and standardized in the second edition of the C&Q Guide, C&Q is an integrated process for establishing that systems are suitable for their intended purpose. Within this C&Q process:

- *Commissioning* is the engineering process for delivering systems that meet established design requirements and stakeholder expectations.
- *Qualification* is the quality process for demonstrating and documenting that critical systems are suitable for their intended purpose.
- *Verification* is any activity that supports those processes and demonstrates that systems are suitable for their intended purpose.

Engineering subject matter experts (SMEs) play an integral role under this model. Process development and technical operations SMEs develop, define, and ensure the technical transfer of product and process knowledge (PPK) during process development. Engineering is responsible for:

- Ensuring that product and process knowledge is incorporated into the user requirements specification (URS)
- Identifying user requirements that impact critical quality attributes and critical process parameters and that contribute to process and system risk assessments
- Completing design development
- Performing design review

Figure 1: SME and quality responsibilities and deliverables in QRM-based integrated C&Q.



In sum, engineering is responsible for implementing the risk control strategy—that is, ensuring that critical design elements (CDEs) of the system identified through risk assessment are satisfied by the design. As a result, engineering is a key contributor to development of the design qualification (DQ) based on the final approved design. During C&Q, engineering SMEs develop the C&Q plan; perform vendor assessments where they could be beneficial; develop, approve, execute, and review verification testing; and manage discrepancies and changes. Engineering personnel/SMEs then develop the acceptance and release reports.

Under this model, quality personnel have an oversight role with the following responsibilities:

- Ensuring that the C&Q process uses product and process knowledge
- Ensuring that the critical quality attributes and process parameters are incorporated into the user requirements specification
- Approving the risk assessment, including the identification of critical aspects (CAs) and the acceptability of residual risk
- Approving the identification of critical design elements and their acceptance criteria
- Ensuring that testing and documentation are commensurate with risk by approving the C&Q plan, vendor assessments, verification testing deviations involving critical aspects and design elements, and acceptance and release reports

In Figure 1, the responsibility of engineering is apparent. Engineering is responsible for delivering systems fit for the intended purpose, including developing, executing, reviewing, and approving all testing and documentation required to deliver those systems and documenting their fitness for purpose. This model does not differentiate testing for C&Q testing from other testing; all testing is verification—that is, all testing contributes to demonstrating and documenting that systems are fit for their purpose.

The benefit of this approach to quality is significant. Once critical aspects and design elements are documented with acceptance criteria in the design qualification, quality personnel can narrow their focus to their most important priority: process risk mitigation that ensures product quality and patient safety. Table 1 summarizes roles, focus, and responsibilities for engineering and quality in QRM-based C&Q.

Table 1: QRM-based C&Q roles and responsibilities for engineering and quality.

	Engineering	Quality
Role	System delivery	Product quality and compliance
Focus	Fitness for intended use	Ensuring that risks to product quality (patient safety) are identified, and adequate controls are proposed to provide an acceptable risk level Ensuring that the designed controls are tested, have been installed, and operate to meet the specifications and support qualification
Responsibilities	Development of URS, design development, design review, installation, verification of the installation and operation vs. the design specifications, engineering change management (ECM), commissioning summary report (testing and documentation)	Approval of the design qualification, test strategy, and acceptance criteria Approval of ECM for direct-impact systems Approval of the equipment qualification and releasing the system to the next stage

Current Industry Practice

There is a considerable gap between the principles set forth in the second edition of the C&Q Guide and current industry practice. Prior to publication of the first edition of the C&Q Guide, industry had not adopted a structured approach to commissioning. Presently, companies typically have no or limited commissioning procedures. Therefore, systems could be "qualified" but would not truly be ready for operations; additional start-up, debug, and engineering runs would be required for a fully functioning process because companies lacked user requirements specification, design review, and adequate understanding of critical aspects.

The first edition of the C&Q Guide presented a model in which a system underwent impact assessment and then was designed, built, commissioned, and qualified [2]. Under this model, systems were intended to be commissioned following GEPs [10]. A system-level impact assessment (SLIA) determined which systems had impact on product quality (classifying systems as having direct, indirect, or no impact), and a component criticality assessment (CCA) determined whether components within a direct-impact system were critical or noncritical to product quality.

The system-level impact assessment and component criticality assessment were "bottom-up" (i.e., from the equipment/system to the product) forms of risk identification focused on the system, rather than on the product and product and process knowledge, which led to binary "yes/no" risk evaluation. In practice, segregating commissioning from qualification testing and introducing a "leveraging" mentality devalued the importance and contribution of GEP to the C&Q process, leading to an inefficient process in which vendor testing (factory/site acceptance testing, etc.) was not considered part of the process. The first edition of the C&Q Guide proposed that engineering documentation be used or "leveraged" to support qualification [2].

In practice, this approach reduced the redundant testing to qualification of critical components in direct-impact systems and evolved into the concept of "leveraging" commissioning testing into qualification testing. As a result, quality personnel required pre- and postapproval of any engineering testing that was intended to be leveraged. Increased documentation scrutiny was often seen as a hindrance to engineering, and engineering testing that was not intended to be leveraged was often viewed as non-value-added.

Even as firms move to adopt QRM-based integrated C&Q, most projects repeat testing in installation/operational qualification (IOQ). This approach is based on legacy practices and reflects the perception that all user requirements specification items designated as "quality" require a clean run test within installation/operational qualification. However, this approach diminishes the manufacturer's ability to use value-added testing and drives up installation/operational qualification hours. A small subset of companies have successfully used an integrated C&Q process to limit installation/operational qualification to a summary report or gap assessment of commissioning with minimal repeat testing. In practice, GEP is generally not viewed as an engineering quality process necessary to support quality and validation. To the contrary, GEP may be followed as a matter of procedure or seen as a non-value-added hindrance to project progress. Additionally, many current C&Q approaches produce a mindset of "We're only in the commissioning stage; systems will be verified during qualification." As result, most engineering SMEs involved in commissioning focus their efforts on system aspects that do not impact product quality, which is the opposite of where engineering SME efforts *should* focus.

In general, GEP systems are lacking in robustness, maturity, implementation, compliance, or all of these, and are therefore not suitable for underpinning a QRM-based integrated C&Q approach. Furthermore, when the quality unit lacks trust in GEP as an engineering quality system, it requires use of its own quality systems, such as quality change control in lieu of engineering change management (ECM), to provide appropriate oversight and control of all C&Q activities. The end result is additional, less-efficient, more costly processes and additional documentation, testing, and effort with no commensurate, additional reduction or mitigation of product quality risk.

However, capital project timelines are shrinking due to the accelerated approval process, Agile manufacturing, and pressure to shorten the time to market. Corporate engineering is challenged to deliver projects in record time. The typical phase-gate model is being replaced by Agile and value-engineering approaches, and there is much less tolerance for repeated testing and issue discovery during start-up, debug, and engineering runs.

THE COST OF POOR (ENGINEERING) QUALITY

So, what happens when engineering testing is considered insufficient for C&Q needs? The following are some real-world examples:

- Protocol development is driven by the turnover package (TOP) rather than by the risk control strategy (i.e., identified critical aspects and design elements). In one case, a turnover package deemed acceptable by engineering was considered unacceptable by the validation team. That team then took a "We cannot start protocol generation until the turnover package is ready" stance, resulting in delayed protocol generation that immediately affected the overall project schedule.
- Discrepancies that do not impact product quality increase overhead. Issues that have no impact on product quality, such as incorrect make or model number, may be among the discrepancies observed during engineering verification testing. Documenting these issues requires multiple-page forms with multiple steps and signatures, but the ultimate conclusion is "As-installed meets requirements; update the specification." Such quality oversight does little to resolve these discrepancies but adds considerable churn and time to the project.
- Execution schedules are delayed by unnecessary verification-activity dependencies. For example, performing drawing walkdowns and generating redlines during field walks months after receipt and installation can result in quality determining that operational qualification cannot start until

installation qualification is complete. This causes delay while drawing review and updates are completed.

- Critical execution paths are driven by systems with no impact on product quality. Some stakeholders believe that functional or operational verification (traditionally called "operations quality") cannot start until all predecessor systems are "qualified." For example, a company may presume that all feed and intermediate systems in a pharmaceutical water train (municipal water supply, soft water, reverse osmosis water, water for injection) must be qualified as a prerequisite to qualifying a clean steam generator.
- Non-value-added redundant testing is done. For example, when continuity and loop checks performed by the electrical vendor lack appropriate documentation or are not approved by quality, the C&Q team repeats those checks. Similarly, if in-place loop calibration performed by instrument services through automation is not considered to be valid verification testing, the C&Q or automation team redoes the work.

Many assume that engineering's role is to get the project done, and those working in validation will find the problems and provide the documentation. However, this mindset cannot be maintained. Engineering must embrace the efficacy and efficiency gained through a robust GEP-based engineering quality system to deliver facilities, utilities, equipment, and systems that are demonstrated and documented to be suitable for their intended purpose.

BUILDING TRUST BETWEEN ENGINEERING AND QUALITY

Building trust between engineering and quality personnel may require both procedural and cultural change for those in engineering and a paradigm shift for those in quality. All stakeholders must regard GEP systems to be a good business practice that ultimately delivers the project faster and with fewer issues; these systems are a critical component of QRM-based integrated C&Q.

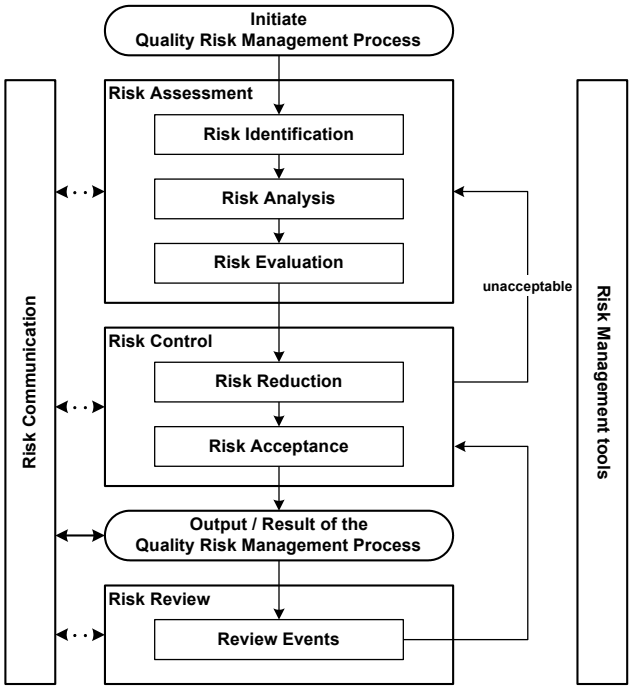
Systems may need to be developed or matured—a spreadsheet on an engineer's computer is insufficient for ECM. The suitability of GEP systems to support and enable QRM-based integrated C&Q may need to be demonstrated through trials or pilot projects assessing engineering product quality. And the quality unit will need to change from a project quality control mindset to a project quality assurance mindset.

The good news is that, in most cases, both engineering and quality personnel welcome and desire this change. Engineering wants to deliver systems that meet requirements, and the quality unit wants to focus on product quality instead of having their efforts diluted by overseeing aspects of project delivery that do not impact product quality.

THE INTEGRATION OF QRM AND GEP

To understand the importance of engineering SMEs and the application of GEP, one must first understand how QRM impacts the C&Q process.

Figure 2: QRM process overview. Reprinted from ICH Q9 [4, p.4]. © European Medicines Agency, 2015.



Background on the QRM Process

QRM is a holistic process in which management policies, procedures, and practices are systematically applied to the tasks of analyzing, evaluating, and controlling risks (see Figure 2). Risk assessment, which is perhaps the most familiar part of the QRM process, includes the identification, assessment, and evaluation of risk to product quality and patient safety. Risk identification answers the question, "What could go wrong?" Risk control involves decision-making to reduce or accept the level of qualified or quantified risk. Risk reduction is the process of mitigating or avoiding identified risks by reducing severity, decreasing the probability of occurrence, or increasing the likelihood of detection. Applied to a manufacturing process, QRM results in the definition of a risk control strategy—the collective design controls, alarms, and procedural controls implemented to mitigate or avoid unacceptably high risk to product quality or patient safety.

Identifying risks to product quality and patient safety requires product and process knowledge, namely the understanding of critical quality attributes and process parameters. Risk to product quality is defined as a failure to meet a product's critical quality attribute, and a process risk is defined as a failure to maintain a critical process parameter. Thus, product and process knowledge, as critical quality attributes and process parameters, is the input to risk assessment. Following the application of risk control, critical aspects, which

Table 2: GEP and QRM perspectives on the purpose of design review.

GEP Perspective	QRM Perspective
• All requirements, including product and process user requirements, general user requirements, and federal, state, and local regulatory code compliance requirements, are satisfied by the design. • Health, safety, and environmental risks are identified and appropriately mitigated by the design. • Business needs, energy efficiency, total cost of ownership, constructability, and other similar considerations are addressed by the design.	• Product and process requirements are satisfied by the design. • Critical aspects are appropriately addressed by the design. • Risks to product quality or patient safety posed by the design are identified. • Unacceptable risks to product quality or patient safety are mitigated by the design.

collectively mitigate unacceptable risk to product quality, become the output of risk assessment (i.e., the risk control strategy).

As QRM is applied to process design, critical aspects are used to develop critical design elements (design features or functions of an engineered system that are necessary to consistently manufacture products with the desired quality). As QRM is applied to C&Q of a system, identification of critical design elements informs the verification strategy, such that these elements are tested commensurately with risk to product quality and patient safety, to verify that their installation and operation are fit for their intended purpose and that system critical aspects are met.

GEP Objectives

GEP, which includes elements of project management and project controls, ensures the following:

- Systems are specified, designed, and installed and operate in a manner that meets operational, maintenance, safety, health, environmental, ergonomic, industry, statutory, and regulatory requirements—including GxP requirements.
- Process risks to product quality are identified, assessed, and mitigated in system design, installation, and operation.
- Appropriate planning, specification, design, installation, verification, acceptance, and maintenance documentation is created throughout the system life cycle.
- Suitable oversight and control are provided for construction, installation, and execution verification activities.

In sum, GEP systems—including design review, ECM, good documentation practice, document/drawing control, vendor qualification, construction quality, commissioning, issue/punchlist management, and asset management—comprise an engineering quality system that underpins the QRM-based, integrated C&Q process. Appropriate engineering SMEs define system requirements and specify, design, and verify the system in an efficient, effective, integrated approach. When a robust engineering quality system built on GEP is implemented, the quality unit and its related quality systems—including quality change control, good documentation practice, document control, deviation management, corrective and preventive action, etc.—can properly focus on product quality and patient safety.

Let's review some of those GEP elements and their relationships to QRM.

Design Review and Verification

According to ASTM E2500 [6], design reviews are:

> *Planned and systematic reviews of specifications, design, and design development and continuous life-cycle of the manufacturing system. Design reviews evaluate deliverables against standards and requirements, identify problems, and propose required corrective actions.*

The purpose of the design review can be considered from two perspectives: GEP and QRM (see Table 2).

The C&Q Guide (§5.3.3, Design Review Process) states [9]:

> *The effort, formality, and documentation of DRs [design reviews] should follow the ICH Q9 principles of being commensurate with the level of risk. DR documentation may take the form of engineering meeting minutes or notes. For highly critical systems, DRs may be more focused and detailed.*

Per ASTM E2500 [6], verification is:

> *A systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as qualification, commissioning and qualification, verification, system validation, or other.*

As such, verification, like design review, can be considered from GEP and QRM perspectives.

- From the GEP perspective, verification includes fitness for intended use for all aspects of a system and encompasses both requirements that impact product quality (product/process user requirements) and requirements that do not (general user requirements).

- From the QRM perspective, verification includes fitness for intended use for critical aspects of a system and encompasses product/process user requirements only. As with design review, the scope of verification activities should be commensurate with the level of risk.

So, how does design review enable QRM-based, integrated C&Q? First, design review minimizes implementation of systems that fail verification testing by ensuring that the design satisfies user requirements prior to procurement or fabrication of the system. As a result, changes, redesigns, and rework during system commissioning are minimized.

Second, design review helps ensure that user requirements are well defined and appropriate. To perform verification, user requirements—and therefore the design aspects that satisfy those user requirements—must be specific, realistic, measurable, and verifiable. Verifying these aspects of the design through design review supports and facilitates verification of the system once implemented.

Third, and most importantly from the QRM perspective, design review supports definition of the process risk control strategy and identification of the system's critical aspects. Design review identifies process risks to product quality posed by the design and determines the acceptability of those risks. Where identified risks are unacceptable, design review ensures that the design acceptably mitigates those risks. Thus, the design features that mitigate risk to product quality are identified as critical aspects, which, when combined with risk assessment, directly inform the verification strategy to ensure that testing is commensurate with risk.

Engineering Change Management

ECM is an established engineering procedure for managing proposed changes, including request, impact assessment, implementation planning and execution, implementation verification, documentation, request closure, and follow-up. It is a system life-cycle process that begins at system definition and continues through design, verification, operation, and decommissioning. ECM ensures that, through defined processes, proposed changes are assessed for project or operational risk, assessed for impact on product quality and patient safety, and implemented in a manner that is managed, tested, and documented commensurately with assessed risk.

From the GEP perspective, ECM offers a change-implementation process that is scaled to risk, complexity, and system life-cycle change, ensuring controls are appropriate to the assessed risk. Prior to system acceptance, proposed changes to project requirements or design specifications are assessed for impact to project scope, cost, and schedule. After system acceptance, proposed changes to operational assets are assessed for their impact on operation and maintenance.

From the QRM perspective, ECM ensures that quality oversight for direct-impact systems is applied to changes affecting critical aspects that are proposed after the design has been accepted through design qualification. After the system is qualified, subsequent changes are managed through the quality (or operational) change control system.

ECM enables QRM-based integrated C&Q in several ways. ECM ensures that the impact of proposed changes on system requirements is identified, assessed, and controlled. During verification activities, ECM ensures that testing and documentation related to implementation of proposed changes are managed and controlled. ECM supports QRM for direct-impact systems by ensuring that risks to product quality related to proposed changes are identified, assessed, evaluated, and controlled to an acceptable level; that quality oversight of proposed changes is appropriate for the system life-cycle stage; and that implementation of proposed changes is tested in a manner commensurate with risk to product quality and patient safety. ECM enables quality oversight to focus on changes to the system's critical aspects and design elements that have the potential to affect product critical quality attributes.

Engineering Quality Process

An engineering quality process (EQP) is a subset of the overall quality management system (QMS) that provides and addresses quality practices for C&Q. An EQP is a philosophy rather than a collection of tools and templates, and, like the overall quality management system, it emphasizes product quality rather than regulatory compliance. The EQP establishes or references the QRM process for C&Q; provides the basis for sustainable, consistent, cost-effective, and practical engineering processes for project and operational life-cycle management; and plays a significant role in providing the practices and controls within the facilities and equipment quality system, which is one of the six systems included in the US FDA Drug Manufacturing Inspection Compliance Program's "Six System" inspection model [11].

From the GEP perspective, the EQP does the following:

- Provides a systematic structure to define, develop, and implement efficient and streamlined engineering processes
- Delivers systems that are fit for intended purpose
- Enables the assurance of quality and compliance with policies, regulations, and standards
- Reflects the scope of the C&Q program and provides associated tools and templates
- Incorporates technical expertise and best practices

From the QRM perspective, the EQP:

- Underpins efficient implementation of a science- and risk-based approach to facility start-up
- Enables science- and engineering-based decisions for C&Q testing
- Delivers systems with product quality risk sufficiently managed through application of engineering standards and practices

An EQP enables QRM-based integrated C&Q through documented activities during system life-cycle stages and supporting systems

An engineering quality process emphasizes product quality rather than regulatory compliance.

throughout the system life cycle. During design and procurement, EQP manages vendor/supplier management. During construction/system implementation, EQP manages construction quality, commissioning, and handover. During routine operation, EQP manages asset management, calibration, and maintenance. Throughout the system life cycle, EQP manages document and drawing control, issue and punchlist management, and engineering good documentation practice.

An EQP ensures that product quality requirements are incorporated into system requirements. During specification and design, an EQP ensures that design decisions and design review outcomes are traceable and can be evaluated. During verification, an EQP ensures that testing activities and documentation are suitable for use as verification and are commensurate with risk. During system acceptance and release, an EQP ensures that a system's fitness for its intended use can be determined from engineering testing results.

CONCLUSION

Under the QRM model, all testing adds value as verification activities, testing is commensurate with product risk, GEP and engineering SMEs are emphasized in the process, and quality is focused on the identification, mitigation, and control of risks to product quality, as well as verification of the process risk control strategy. Under this model, GEP as an EQP enables the C&Q process.

As a result, systems are designed and delivered to specification more reliably, with reduced costs and shorter schedules. Issues are resolved and changes are managed faster, more efficiently, and with greater cost efficiency. Verification testing activities are performed more efficiently and result in more robust, science- and risk-based documentation of fitness for intended use to produce products that meet quality requirements.

In partnership with ISPE, CAI is engaged in a long-term effort to develop industry benchmarking data to assess maturity of QRM-based integrated C&Q programs and to provide a roadmap for firms interested in following current industry best practices. Additional data will be collected and trended over time. CAI will continue to report on industry progress, and participating firms are provided access to the full data set.

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Additional Resources

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SOLUBILITY ENHANCEMENT OF IBUPROFEN

by Porous Solid Dispersion Using a Flash Evaporation Method

By Shmmon Ahmad, Anil Kumar, Abdul Hafeez, PhD, and Rupinder Kaur, PhD

The solubility behavior of drugs remains one of the most challenging aspects of formulation development and is a key determinant of a drug's bioavailability. This article describes research aimed to improve solubility of a poorly water-soluble drug (ibuprofen) by preparing a porous solid dispersion using a flash evaporation technique.

Solubility, the phenomenon of dissolving a solute in solvent to create a homogenous system, is an important parameter to achieve the drug concentration in systemic circulation required for the desired (anticipated) pharmacological response [1]. Solubility is among the most vital physicochemical properties of a drug, and the bioavailability of an orally administered drug depends primarily on its solubility in the gastrointestinal tract and its permeability across cell membranes [2]. Oral ingestion is the most common and convenient route of drug delivery because it is easy to administer drugs orally and because the drugs designed for the oral route offer advantages such as stability, accurate dosage, and easy production.

Most drugs are administered in a solid form, and low aqueous solubility can either delay or limit drug absorption. Drugs that are lipophilic may fail to reach market due to their poor aqueous solubility. Enhancing solubility is therefore a major challenge in formulation development of new chemical entities, including generic drugs. Fortunately, formulation scientists can use different technological approaches to resolve this challenge [3].

After screening physicochemical and biopharmaceutical properties of various drug candidates, ibuprofen was selected for the present study due to its poor bioavailability after oral administration. Ibuprofen is often administered in a solid oral dosage form with a high dose (200–800 mg). It is a Biopharmaceutical Classification System class II drug (aqueous solubility <0.1 mg/mL). Various techniques such as particle size reduction, crystal habit modification, complexation, solubilization, solid dispersion in carriers, and salt formation have been employed to improve the aqueous solubility of class II drugs. Solid dispersion can be achieved with spray-drying, hot-melt extrusion, supercritical fluid, and cryogenic freezing technologies. However, these technologies (especially supercritical fluid and cryogenic freezing) are limited in their ability to scale-up [4].

SOLID DISPERSION METHODS

Solid dispersion is defined as the mixing of one or more active ingredients in an inert carrier or matrix at solid state. It can be prepared by the following methods (see also Figure 1):

- Hot-melt extrusion [5–7]
- Spray-drying [8]
- Fluid bed coating [9]
- Freeze-drying (lyophilization) [10, 11]
- Hot spin mixing [12]
- Dropping method [13]
- Supercritical fluid process [14]
- Solvent or melting-solvent method [15]
- Flash evaporation [16]

FLASH EVAPORATION

In the flash evaporation technique, a boiling concentrated solution of the poorly water-soluble drug and a water-soluble carrier in a suitable nonaqueous solvent is subjected to sudden vacuum, resulting in flash evaporation and the formation of a porous mass that, upon grinding, yields porous granules. Adeyeye and Barabas find that this technique has more advantages than other solid-dispersion techniques [17].

When a nonporous mass is brought into contact with water, only the surface portion is in direct contact with water and subject to dissolution. As one surface dissolves, another comes into

contact with water, and the dissolution process continues until the entire mass dissolves [18].

Dissolution Mechanism for a Nonporous Mass

Nonporous mass in contact with water ➔ dissolution is limited to the surface ➔ dissolution proceeds ➔ entire mass is in solution

In contrast, dissolution of a porous mass is much faster. The pores in the mass act as capillaries due to surface force, and liquid is drawn into these capillaries spontaneously—a phenomenon called "capillarity."

This phenomenon can be expressed by following equation [19]:

$$h = \frac{2\gamma\cos\theta}{dgr}$$

where h is the height above the liquid to which the liquid rises in a capillary, r is the radius, d is the density of the liquid, γ is the surface tension of water, ϑ is the angle of contact, and g is the acceleration due to gravity.

The height to which water rises in a capillary depends on the capillary radius. Employing this principle to penetration of water inside pores, the depth of penetration depends on the pore diameter. When water penetrates a porous mass, an enormous surface is in contact with water and, consequently, dissolution is expected to be rapid.

Dissolution Mechanism for a Porous Mass

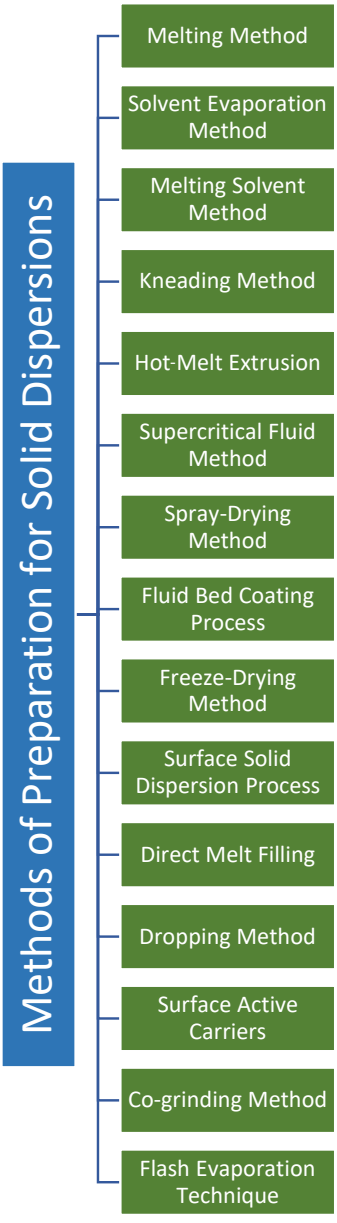
Porous mass in contact with water ➔ dissolution is not limited to the surface ➔ dissolution proceeds (breakdown) ➔ entire mass is in solution

Increased porosity exposes a greater surface area of the product to the dissolution fluid and encourages penetration and circulation of dissolution fluid into the mass due to capillary action.

Other research suggests that the porous solid dispersion prepared by flash evaporation technique may offer the following advantages [20, 21]:

- Excellent content uniformity
- Steep increase in bulk as well as porosity of the product
- Simplicity in process
- Exceptionally high dissolution rate owing to the combined effect of solid dispersion and capillary
- Option to use expensive carriers because a smaller amount of carrier is required
- Ease in converting the porous mass into granules by grinding to facilitate encapsulations, which decreases in overall product cost
- Greater product efficacy

Figure 1: Preparation methods for solid dispersions.



MATERIALS, METHODS, AND FINDINGS

Materials

Polyvinyl-pyrrolidone (PVP K-30) was chosen as the carrier for the solid dispersions by flash evaporation. Following ICH guidelines for the selection of a suitable solvent for the preparation of solid dispersions, acetone was used as the solvent to prepare the solid dispersions.

We purchased ibuprofen from Helios Pharmaceutical (Baddi, India); PVP K-30 from S D Fine-Chem Limited (Mumbai, India); methanol from Merck Limited (Mumbai, India); ethanol from

Rankem (Gurugram, India); ethyl acetate and acetone from Barna Chemicals (Vadodara, India); 2-propanol and 1-propanol from Triveni chemicals (Vapi, India); and potassium dihydrogen orthophosphate from Fisher Scientific (Mumbai, India). All other materials used were of analytical grade.

Preparation of Ibuprofen Solid Dispersion by Flash Evaporation

We prepared solid dispersion of ibuprofen with PVP K-30 using a 10% concentration of the drug to the total weight of the carrier. First, 400 mg of ibuprofen were placed in a round-bottom flask, and then 8 mL of acetone was added to dissolve it. Next, 4 g of PVP were added to the solution, with constant stirring, to obtain uniform distribution of the drug in the viscous solution. The viscous solution was heated until it reached its boiling point and subjected to vacuum at 760 mmHg to yield porous solid dispersion and then collected in a beaker. The resultant dry porous solid dispersion was passed through sieves no. 22 and no. 44, and granules retained on sieve no. 44 were used further to characterize and evaluate solid dispersion.

Optimization of Solid Dispersion

The following factors affecting expansion ratio, bulk density, and porosity were studied to evaluate porous solid dispersions created with the flash evaporation technique:

- Solvent volatility
- Carrier–solvent ratio
- Vacuum
- Drug–carrier ratio

Solvent Volatility

To study the effects of solvent volatility, only the polymer was used. In each test, investigators dissolved 4 g of PVP K-30 in 8 mL of a solvent and heated the solution until it boiled. The boiling concentrated solution was subjected to sudden vacuum at 760 mmHg to yield a porous mass. The bulk volume of the porous mass was noted in terms of expansion ratio and percentage porosity. The dry product obtained from the test was crushed and passed through no. 22 and no. 44 sieves. Granules retained on sieve no. 44 were used to calculate bulk density and porosity (Table 1).

Table 1: Effect of solvent volatility on the expansion ratio, bulk density, and porosity.

Sr. no.	Solvent	Boiling Point of Solvent (°C)	Expansion Ratio	Bulk Density (g/mL)	Porosity (%)
1	Ethanol	78.5	6:1	0.240	79.56
2	Methanol	64.6	4:1	0.212	81.21
3	Ethyl acetate	77.0	3:1	0.169	86.14
4	Acetone	56.2	8:1	0.142	89.42
5	2-Propanol	82.4	5:1	0.175	80.75
6	1-Propanol	117.6	5:1	0.249	78.34

Carrier–Solvent Ratio

To study the impact of relative proportions of carrier and solvent, 4 g of PVP K-30 were dissolved in the minimum proportion of solvent (8 mL of acetone) in a round-bottom flask. The flask was heated, and then the boiling concentrated polymer solution was subjected to sudden vacuum at 760 mmHg to yield a porous mass. The bulk volume of the porous mass was noted in terms of expansion ratio.

The resultant dry porous mass was crushed and passed through sieves no. 22 and no. 44. Granules retained on sieve no. 44 were used to determine bulk density and porosity. The same process was repeated using increasing volumes of acetone for the same quantity of PVP K-30 (Table 2).

Table 2: Effect of relative proportion of carrier to solvent on the expansion ratio, bulk density, and porosity.

Sr. No.	Carrier–Solvent Ratio	Expansion Ratio	Bulk Density (g/mL)	Porosity (%)
1	1:1	7:1	0.096	90.85
2	1:1.5	6:1	0.168	85.42
3	1:2	9:1	0.064	95.34
4	1:2.5	5:1	0.154	89.66
5	1:3	4:1	0.139	88.56

Vacuum

To evaluate the effects of vacuum, 4 g of PVP K-30 were dissolved in 8 mL of acetone and heated. Then, the boiling concentrated solution of PVP K-30 was subjected to sudden vacuum at 760 mmHg to yield a porous mass. The bulk volume of the porous mass was then noted in terms of expansion ratio. The resultant dry porous mass was crushed and passed through sieves no. 22 and no. 44. Granules retained on sieve no. 44 were used to determine bulk density and porosity. The same procedure was then adapted for various vacuum conditions (Table 3).

Table 3: Effect of vacuum on the expansion ratio, bulk density, and porosity.

Sr. No.	Vacuum (mmHg)	Expansion Ratio	Bulk Density (g/mL)	Porosity (%)
1	150	4:1	0.284	75.84
2	300	4:1	0.284	82.59
3	450	7:1	0.179	88.21
4	600	8:1	0.119	90.78
5	760	9:1	0.068	94.98

Drug–Carrier Ratio

Ibuprofen in the ratio of 2.5% (i.e., 100 mg of total weight of PVP) was placed in a round-bottom flask and dissolved in acetone using a carrier–solvent ratio of 1:2. The flask was heated, and the boiling concentrated solution was subjected to sudden vacuum at 760 mmHg to yield a porous mass. The bulk volume of the porous

mass was noted in terms of expansion ratio. The resultant dry porous mass was crushed and passed through sieves no. 22 and no. 44. Granules retained on sieve no. 44 were used to determine bulk density and porosity. Additional porous solid dispersions were prepared by increasing the concentration of drug (i.e., 5%, 7.5%, 10%, 12.5% of the total weight of polymer). Bulk density and porosity of dry porous solid dispersions were determined for all products (Table 4).

Table 4: Impact of drug–carrier ratio on the expansion ratio, bulk density, and porosity.

Sr. No.	Amount of Drug (%)	Expansion Ratio	Bulk Density (g/mL)	Porosity (%)
1	2.5	3:1	0.114	83.45
2	5.0	5:1	0.102	92.58
3	7.5	6:1	0.095	93.56
4	10.0	8:1	0.071	95.78
5	12.5	6:1	0.101	91.97

Summary of Findings

Results shown in Tables 1–4 indicate that a higher concentration of the drug in a porous solid dispersion decreases the product's porosity. After studying Tables 1–4, the additional following conclusions can be drawn:

- The maximum increase in bulk and porosity occurs at the boiling point of the solvent.
- A solvent with a lower boiling point (e.g., acetone) is more suitable for flash evaporation and offers a greater increase in bulk than solvents with higher boiling points.
- A carrier–solvent ratio of 1:2 offers the greatest increase in bulk and porosity.
- Porosity is directly proportional to vacuum, and maximum porosity is obtained at 760 mmHg.
- A 10% concentration of drug maximizes the bulk and porosity of the product.

In sum, the following conditions must be maintained to obtain maximum porosity in the porous solid dispersion:

- Solvent: Low boiling point (acetone)
- Temperature: Boiling point of acetone (i.e., 56.2°C)
- Vacuum: 760 mmHg
- Carrier–solvent ratio: 1:2
- Drug concentration: 10%

CHARACTERIZATION OF SOLID DISPERSION

FTIR Spectroscopy

Fourier-transform infrared (FTIR) spectroscopy studies were performed to evaluate the possible interaction between the polymer and the drug. The FTIR spectroscopy of the solid dispersion spectra of the physical mixture drug with PVP K-30 was recorded for samples prepared by KBr disc method. Spectra were recorded in the 4,000 cm^{-1} to 400 cm^{-1} region [22] and were clearly observed. Ibuprofen peaks were observed at 2,937.59 cm^{-1} corresponding to C-H stretching aromatic.

Additionally, the FTIR spectrum of ibuprofen showed that principal peaks were observed at wave numbers of 511.15/cm to 683.7/cm for aromatic C-H deformation; 772.52/cm for aromatic C-H deformation (two adjacent free Hs); 938.40/cm for aromatic C-H deformation (one adjacent free Hs); 1,074.39/cm for C-N vibration; 1,241.23/cm for C-O stretching; 1,329.00/cm for O-H bend; 1,435.09/cm for C=H deformation (CH_3CH_2); 1,715.74/cm for C=C stretching of α-β unsaturated ring; and 2,942.51/cm for C-H stretching.

Thermal Analysis

A differential scanning calorimetry (DSC) instrument was used for thermal analyses of the pure drug and a physical mixture of the drug and PVP K-30 as a solid dispersion. The sample was heated in a sealed aluminum pan at 10°C per min^{-1} from 0°C to 300°C [23].

When pure ibuprofen was heated from 25°C to 100°C at 10 K/min, the DSC curve showed the melting point to be around 77.87°C (Figure 2). The DSC curve for the porous solid dispersion sample (Figure 3) showed the onset of melting temperature to be 44.99°C, and the melting endothermic peak was recorded at 67.77°C with enthalpy of fusion –157.43 J/g.

Figure 2: DSC curve of ibuprofen.

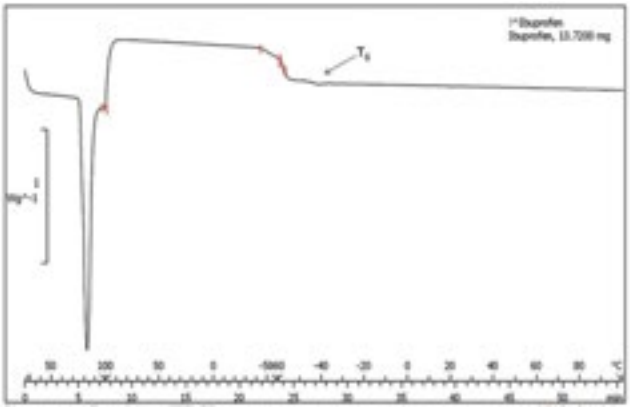


Figure 3: DSC curve of porous solid dispersion.

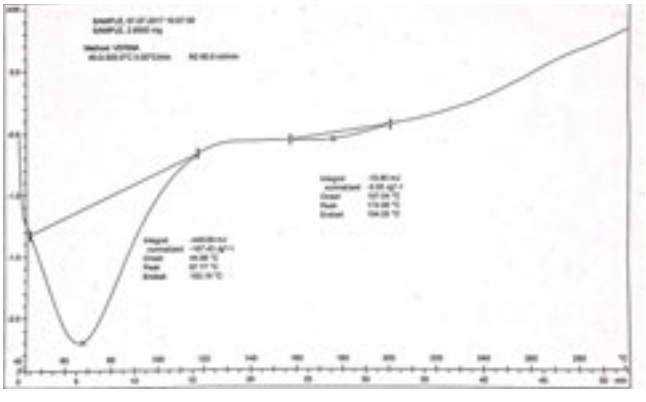


Figure 4: XRD curve of pure ibuprofen.

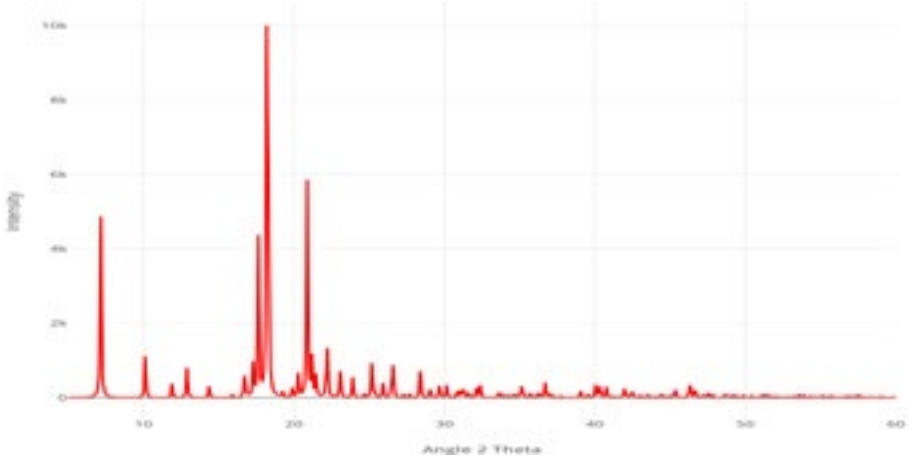
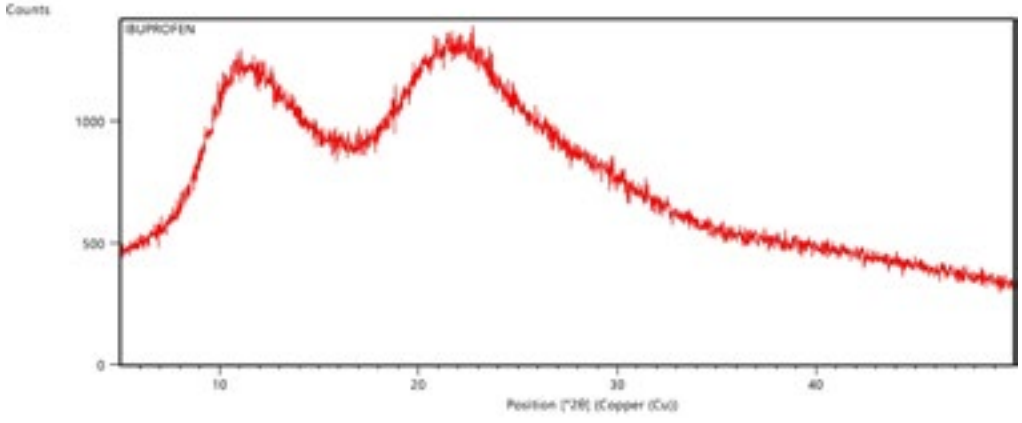


Figure 5: XRD curve of the solid dispersion prepared by flash evaporation.



X-ray Diffraction Analysis

X-ray diffraction (XRD) is frequently used to examine the degree of crystallinity in a sample. We conducted an XRD study using Cu K-α radiation filtered by Ni to characterize the physical form of ibuprofen in selected sample formulations. The samples were analyzed in the range of 2θ = 5°C–50°C. The operating conditions used were voltage 45 kV; current 40 mA; scanning speed 1/min; and temperature of acquisition at room temperature. XRD patterns of pure ibuprofen and the solid dispersion were taken.

Pure ibuprofen showed various characteristically sharp and intense peaks (Figure 4), suggesting that the drug was present as a crystalline state [24]. Figure 5 shows the decrease of drug crystallinity in the solid dispersion.

In Vitro Drug Release

Accurately weighed physical mixtures of prepared formulation, each equivalent to 100 mg of ibuprofen, were added to 900 mL of dissolution medium (PBS pH 7.2) in a basket-type apparatus and stirred at a speed of 50 rpm at 37°C ± 0.5°C. Investigators withdrew 5-mL aliquots at 5, 10, 20, 30, 40, 50, and 60 minutes and replaced each aliquot with 5 mL of fresh dissolution media. The collected samples were analyzed after filtration and dilution at λ_{max} 222 nm using an ultraviolet–visible spectroscopy spectrophotometer against the blank. Drug-release studies were carried out in triplicate. The dissolution studies of pure ibuprofen were performed in a similar fashion. The release profile data were analyzed for the cumulative percentage of drug released at different time intervals [22,25].

In Vitro Drug Release Kinetics

Multiple kinetic models describe the release behavior of drug from the dosage forms. Model-dependent methods are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected, the dissolution profiles are evaluated depending on the derived model parameters [26]. To predict the drug-release pattern of ibuprofen from solid dispersion formulations, the data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

Zero-Order Kinetics

Zero-order release kinetics refers to the process of constant drug release from a drug delivery device such as an oral osmotic tablet, transdermal system, matrix tablet for low-solubility drugs, or other delivery system. In its simplest form, zero-order release can be represented as follows:

$$Q = Q_0 + K_0 t$$

where Q is the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Q_0 is the initial amount of drug in solution (it is usually zero), and K_0 is the zero-order release constant at time t. The graph is plotted as the percentage of cumulative drug release vs. time.

First-Order Kinetics

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism theoretically. Drug release that follows first-order kinetics can be expressed by the following equation:

$$Q_t = Q_0 e^{-kt}$$

or

$$\ln(Q_t/Q_0) = K_1 t$$

where Q_t is the initial amount of drug dissolved at time t, Q_0 is the amount of drug in the solution, and K is the first-order release rate constant. It can be also be expressed as:

$$\log C = \log C_0 - Kt/2.303$$

where C_0 is the initial concentration of drug, k is the first-order rate constant, and t is the time [26]. The data obtained are plotted as log cumulative percentage of drug remaining vs. time.

Higuchi Model

In 1961, Higuchi proposed the first mathematical model to describe drug release from a matrix system [27]. He was the first to derive an equation to describe drug release from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion. The following relation is used to express the Higuchi model:

$$Q_t = K_t$$

where Q_t is the initial amount of drug dissolved in time t, and K is the Higuchi release constant. The graph is plotted as the percentage of cumulative drug release vs. the square root of time.

Korsmeyer–Peppas Model

Korsmeyer derived a relationship that described drug release from a polymeric system. To identify the mechanism of drug release, drug release data were fitted in the Korsmeyer–Peppas model:

$$M_t/M_\infty = Ktn$$

where M_t/M_∞ is the fraction of the drug released at time t, K is the rate constant, and n is the release exponent. The n value is used to characterize specific release mechanisms [28, 29]. The Korsmeyer–Peppas model is plotted as the log cumulative percentage of drug release vs. log time.

Findings

The regression coefficient data obtained from various release kinetics models are as follows:

- Zero-order: y = 1.281x + 28.32; R^2 = 0.789
- First-order: y = 0.017x + 1.900; R^2 = 0.980
- Higuchi: y = 11.73x + 9.216; R^2 = 0.962
- Korsmeyer–Peppas: y = 0.335x + 1.352; R^2 = 0.987

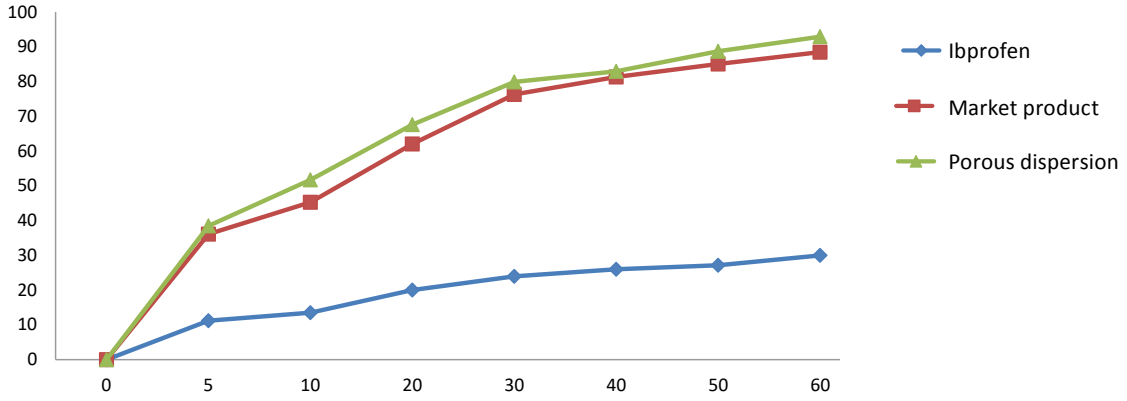
The drug-release kinetic model with the highest regression coefficient value (R^2) was considered to be the drug-release mechanism. R^2 was highest (0.987) for the Korsmeyer–Peppas model, which describes the diffusion of the drug from homogenous and granular matrix systems.

In Vitro Dissolution Rate of Products Containing Ibuprofen

Dissolution Medium

Solubility of ibuprofen in the following dissolution media was evaluated: buffer pH 7.2, 6.8, 4.5, and 0.1 N HCl. Solubility was

Figure 6: Comparison of % drug release of formulations containing ibuprofen.



Porous solid dispersion prepared by flash evaporation had a better dissolution profile than the commercial tablet, and the pure ibuprofen sample had the slowest dissolution rate.

highest (5.85 ± 0.59 with standard deviation [*n* = 3]) in buffer pH 7.2. Solubility was lowest (2.18 ± 0.50 [with standard deviation n = 3]) in pH 1.2 media.

Dissolution

The dissolution medium consisting of 900 mL of phosphate buffer pH 7.2 was placed in the cylindrical vessel of USP dissolution apparatus 2. The apparatus was assembled, and the dissolution medium was heated to 37°C ± 0.5°C before a drug sample was added to the vessel. The sample of solid dispersion granules prepared by the flash evaporation method contained 100 mg of ibuprofen. Additionally, pure drug ibuprofen and a commercially available ibuprofen tablet manufactured using the wet granulation method were tested.

In each test, the paddle was rotated at a speed of 50 rpm and 5-mL aliquots were withdrawn at appropriate time intervals and replaced with 5 mL of fresh dissolution medium. The sample was then passed through Whatman filter paper. The absorbance of the sample was evaluated by UV spectrophotometer at 222 nm. The concentration of ibuprofen in each sample was determined from the standard curve of ibuprofen in phosphate buffer pH 7.2. Percentages of the drug dissolved at various time intervals were calculated (Table 5). Porous solid dispersion prepared by flash evaporation had a better dissolution profile than the commercial tablet, and the pure ibuprofen sample had the slowest dissolution rate (Figure 6).

Table 5: Comparison of ibuprofen-release percentages by dissolution profile.

	% Release of Ibuprofen		
Time (min.)	Pure Ibuprofen	Commercial Product	Porous Solid Dispersion
0	0	0	0
5	11.19	36.12	38.46
10	13.52	45.26	51.68
20	20.01	62.05	67.58
30	23.96	76.25	79.86
40	26.01	81.29	82.91
50	27.12	85.06	88.68
60	29.98	89.46	92.89

CONCLUSION

Flash evaporation techniques can improve the dissolution and bioavailability of low-solubility drugs such as ibuprofen by altering their physical and chemical properties. Solid dispersions provide the means to reduce the drug particle size to a molecular level and homogeneously distribute a small amount of drug in a solid form. This enhances a solid drug product's dissolution rate and content uniformity.

We used various spectrophotometric analyses to evaluate solid dispersions of ibuprofen. The DSC thermogram peak at

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67.77°C indicated the presence of ibuprofen in the porous solid dispersion at the molecular level. The XRD study of the porous solid dispersion showed peaks for pure ibuprofen and PVP K-30, indicating that there was no chemical interaction between the drug and the carrier.

In the in vitro dissolution studies of formulations containing ibuprofen, pure ibuprofen had the slowest dissolution rate. The release of the drug from the porous solid dispersion formulation prepared by flash evaporation was rapid compared to the commercial formulation manufactured using the wet granulation method.

A porous solid dispersion prepared by the flash evaporation technique is easier to grind into granules. Therefore, this method facilitates encapsulation, which decreases overall product cost and increases product efficacy.

Our investigation suggests that the flash evaporation technique can improve the efficacy of the solid dispersion by converting it into porous form. The resulting two-in-one product can greatly enhance the dissolution rate by simultaneously exploiting two techniques: solid dispersion and capillarity. This technique has vast commercial potential for a wide range of drug candidates.

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INDEX

BWT Pharma & Biotech GmbH	7
CAI	Back cover
COPA-DATA	Inside back cover
CRB	1
EI Associates	55
Elettracqua Srl	9
Endress & Hauser AG	17
Fluor Corporation	Inside front cover
Intelligen, Inc.	11
Jacobs	3
Kneat Solutions	15
Peacock Engineering Ltd.	37
SPIRAX SARCO	5
ValGenesis, Inc.	35

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