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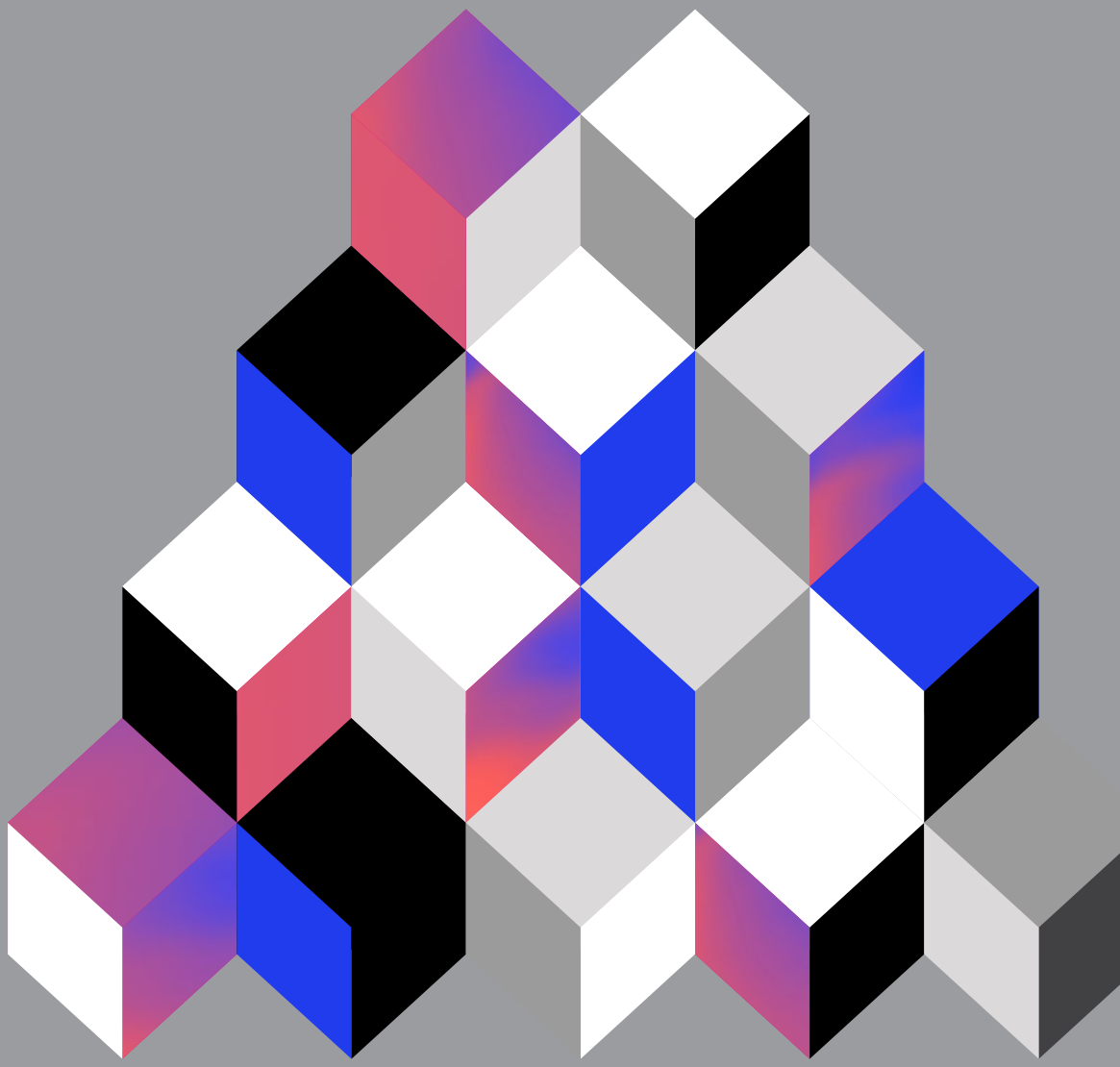

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Volume 42, Number 4

ISSN 0273-8139
Pharmaceutical Engineering is published six times a year by ISPE and is online at ISPE.org/Pharmaceutical-Engineering

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Art Direction and Graphic Design
THOR Design, Inc., www.thor.design

Printing
Royle Printing

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US Postmaster
Send change of address to:
Pharmaceutical Engineering Magazine
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Periodicals postage paid at Tampa, Florida, US, and additional post offices

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By Jörg Zimmermann


Jörg Zimmermann

The Value of Volunteering

Why do I volunteer at ISPE? It is a question that I and surely many of you get asked. Indeed, why?

On the ISPE International Board level, we embarked on the exercise of writing down the ISPE value proposition, and under the leadership of Vivianne Arencibia, one of our Directors, this was put to paper. It all sounds so obvious, but when you look at all the great offerings that ISPE has, the question becomes: Why don't more pharmaceutical industry professionals volunteer at ISPE?

The value proposition will be the basis of your elevator speech: How can I put my motivation to volunteer at ISPE into 30 seconds (i.e., a typical elevator ride) and convince my counterpart to join?

A VOLUNTEER'S JOURNEY

Let me tell you how it started for me. I was invited to give a talk on lyophilization at a European conference in Zurich in 2000. I had a great time discussing the topic with peers and we had great experts at that conference sharing their knowledge. What I had to report was well received and I was invited to further conferences in Europe and the US. After a few conferences, I was asked to put together a track for the 2011 ISPE Tampa Conference on prefilled syringes. We had a great program but low attendance, so I thought that's it, they are not going to invite me back. Instead, I continued as Track Leader and later was "promoted" to Co-chair the full conference! After that, there was no stopping: I got involved as a reviewer of articles for *Pharmaceutical Engineering*®, joined the steering committee of the Sterile Products and Processes Community of Practice, led that committee for a few years, and later was elected to the ISPE International Board of Directors.

So, why am I doing this? ISPE has developed over the years to become such an influential organization that we are truly shaping the future of the pharmaceutical industry. Being part of that, and working for the benefit of the patients, is both rewarding and fun!

THE VALUE PROPOSITION

Volunteer work is a challenge for many as it comes on top of your day job and you always have to balance. We understand that, and it happens that people will drop out of volunteer jobs at very short notice. It happened to me one time when my conference co-chair resigned with a day's notice. Luckily, we had a robust program committee to compensate.

The more you put into your volunteer work, the more you get out of it: education, knowledge, networking, tangible information for your day job—it is all there!

A value proposition describes the benefits and offerings of an organization, and how the organization is different from others. One of the differentiators for me is ISPE's spirit. ISPE members are always open to share and contribute, and over the years, this has become a circle of friends and a home.

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The more you put into your volunteer work, the more you get out of it: education, knowledge, networking, tangible information for your day job—it is all there! ISPE members are always open to share and contribute, and over the years, this has become a circle of friends and a home.

WHAT ARE THE ELEMENTS OF THE ISPE VALUE PROPOSITION?

ISPE members uniquely benefit from professional growth and knowledge sharing on industry best practices, through innovative forums bringing together ISPE's network of more than 19,000 members at local and international levels. ISPE members stand front and center in steering the future state of the global pharmaceutical industry.

AS A MEMBER OF THE ISPE COMMUNITY, YOU WILL:

Develop and maintain your technical skills and knowledge through best-in-class educational offerings.

ISPE's education offerings include conferences, workshops, webinars, and classroom trainings. The content is designed for all stages of your career, whether you are new to the industry or a seasoned professional. There is a plethora of publications—this magazine in print and digital; SmartBrief; the *Regulatory Digest* newsletter; Women in Pharma® *The Bridge* newsletter; and the gold-standard guidance documents where you can find the combined knowledge of ISPE's members. Extensive vendor and industry information on new and innovative technologies is also available through online white papers, sponsored content, the online Partner Showcase, Virtual Discovery Stage, and more.

Advance and shape the current and future state of the industry, foster innovation, and address global and local needs unique to our industry.

Volunteer opportunities are available at all stages of your career, for students, new professionals, mid-career, and senior leaders. You can volunteer at local and international levels and participate in various forums in interest groups and activities in various areas, including:

- Emerging Leaders
- Women in Pharma®
- Workforce of the Future
- Pharma 4.0™
- Student Hackathons

Gain practical knowledge, problem solve, and grow your network as part of ISPE's diverse global membership of pharma industry professionals, academics, and regulators.

ISPE gives you access to member-only Communities of Practice (CoPs). There are currently more than 20 CoPs on various topics where you can share your knowledge and ask your questions. This is where the ISPE community excels, and you will find answers that you can apply to your everyday work problems.

ISPE includes 26 ISPE Affiliates throughout the world and 13 US Chapters as of this writing, each with local activities and offerings for their members often in their local language. This is a big plus for members who cannot travel to the international events.

Members also have access to the ISPE Member Directory of more than 19,000 members from 129 countries across the globe.

Foster your professional growth, expand your leadership skills, and showcase your knowledge.

ISPE Guidance Documents, ISPE Concept and Discussion Papers, and regulatory discussion groups and commenting opportunities on draft regulations will help you in your personal growth and help shape the future of our ecosystem, the global pharmaceutical industry.

ISPE has been instrumental in defining the fields of GAMP®, PQLI® (product quality life cycle implementation), Quality Culture, and how to deal with drug shortages.

And finally, let's not forget the educational and philanthropic goals of the ISPE Foundation, which I talked about in my May-June 2022 column in PE.

BASED ON WHAT YOU HAVE READ, WHAT IS YOUR ELEVATOR SPEECH?

While summer is here, the preparations for the ISPE Annual Meeting & Expo in Orlando, Florida, are in full swing. In addition to a first-class education program, you can also expect fantastic networking and social events, and the opportunity to connect with leading vendors in the exhibit hall.

I hope to see you there in person!

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

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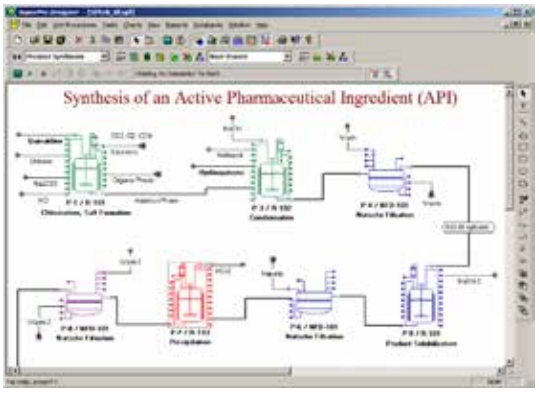

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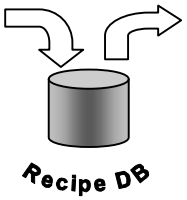

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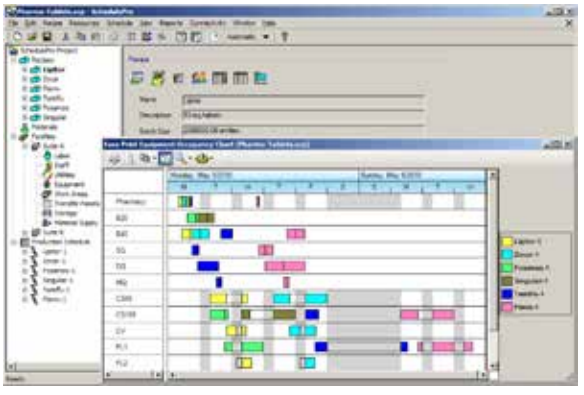
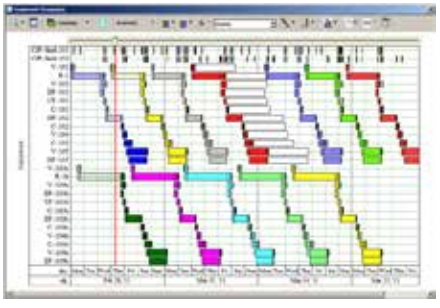


Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



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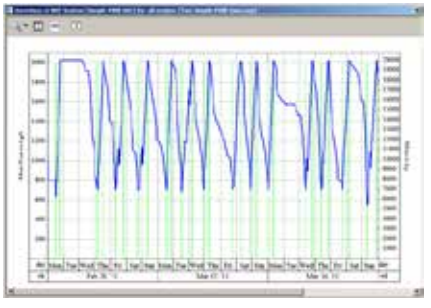

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SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor,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

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By Jennifer Lauria Clark


Jennifer Lauria Clark

ELEVATE YOURSELF WITH KNOWLEDGE—OR SOMETHING ELSE

Knowledge management is powerful. It can be a catalyst for organizational success and create a major competitive advantage, or be a major contributor to organizational failure. We live in a world today where knowledge is literally at our fingertips. To access knowledge in quite literally any topic, we Google it. Merriam-Webster has even added the word "google" as a verb to the dictionary.

I'm going to narrow our focus today and share my thoughts on how you can become a female leader in knowledge management (KM) by branding yourself as a thought leader. A thought leader is perceived as an authority in their domain. These people are seen not only as experts in their field, but also as inspiring leaders who help influence people in positive directions. I believe each of us has the potential to be a thought leader.

Statistics do not lie. According to Texas Woman's University, women make up 50.8% of the population; earn 59% of master's degrees, 48.5% of law degrees, 47.5% of medical degrees, and 38% of MBAs; and account for 47% of the US labor force [1]. However, the highest positions of leadership in the academic, legal, corporate, and political spheres are not held by women. By being an active member of ISPE's Women in Pharma®, we can be significant contributors in the collaboration needed to close this gap. How? Through thought leadership.

FINDING VALUE IN EVERYONE

Princess Diana is thought of as one of the most influential thought leaders in history. Her actions, belief system, and integrity positioned her to bring attention to social causes and challenge public perception through humanitarian efforts. Princess Diana led by example as she fought the stigma against HIV/AIDS patients and extended compassion to leprosy sufferers. She believed everyone needed to feel valued and she shared that value with others. Through her royal status, Princess Diana became a force in the philanthropic community as she shifted perspectives and challenged the status quo, and most important, she inspired others to do the same.

SHAPING THE FUTURE OF PHARMA

You too can take a leap of faith! Put yourself out there and talk about subjects that matter to you. You could host a webinar in your Chapter or Affiliate about inclusivity, speak on a global WIP webinar about sustainability, or lead a think tank series. Your voice matters, and you can be an agent of change.

You can start today by:

- Believing in yourself
- Suggesting an ISPE/WIP webinar
- Joining an executive training for women
- Participating in ISPE Engage
- Asking your leadership to be more involved in your company's operations and functions
- Taking on more visible and challenging tasks
- Promoting the success of other women
- Finding a sponsor or mentor
- Joining ISPE's WIP

I'll leave you with this: Be bold, take risks, and put yourself out there. Elevate yourself with the choices you make, the knowledge you share, and how you share it. You have the potential to be a thought leader, and you deserve recognition for your hard work.

Reference

1. Texas Woman's University. "Thought Leadership & Why It Matters." https://twu.edu/language-culture-gender-studies/thought-leadership/thought-leadership--why-it-matters/

Jennifer Lauria Clark is Vice President, Sales and Account Relationship Management, at CAI, and the ISPE Women in Pharma® 2021–2022 Steering Committee Chair. She has been an ISPE member since 2003.

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By Heather Bennett-Kelley


Heather Bennett-Kelley

SEEING OPPORTUNITY—AND PURSUING IT

When opportunity presents itself, how do we know? And who is the opportunity for? How do we evaluate and determine if it is a "good" opportunity? What needs to line up in order to point all the arrows to "yes"?

What did we do for this opportunity to arise? Did we search it out? Did we prepare ourselves for years through education, training, and positioning? Or did we just put our head down and someone saw that we put in the work? Is it purely because of an alignment of passion, thought process, and being in the right place at the right time? Or did something else not work out, and that freedom allowed for other options? How do we see an opportunity when it comes up?

I've had plenty of opportunities in my life, some of which I didn't see until years later. One pivotal opportunity came because I had some forethought; actually something that was imparted to me by industry mentors, but the important thing is that I listened.

SETTING THE STAGE

I had a feeling that I needed to connect with industry prior to graduation and before I needed to be applying for jobs. I wasn't really sure where the key connection was going to come from, so I leaned in to learn more. In my junior year as an undergraduate chemical engineering student, I was elected Vice President of the ISPE San Jose State Student Chapter. I attended a dinner meeting of the ISPE San Francisco Bay Area Chapter's CEO Night.

I met the Chapter manager and asked how I could best set myself up for a career in industry. They told me to get involved, and so I did. In addition to leadership in the student chapter, I volunteered for the SF Vendor Night committee, and joined the SF Chapter relay team raising money for Organs R Us and awareness for the need for organ donation. I tried at every chance to bring my classmates and colleagues along for the ride, but not everyone understood the value. It paid off in the summer after graduation when I received a call from an industry member I had met as a student. They were looking to fill a position, and when another industry member that I had worked with in ISPE recommended me, they remembered me and made the call.

> One key to being able to see opportunity, or being able to say "yes," is to be open—to possibility and to learning or expanding your experience.

So, in my case, I set the stage for the opportunity years before. I was headed down two parallel paths, nuclear and pharmaceutical, and because I engaged, ISPE chose me. Of course, I had to say "yes" in order to end up where I am today.

SEEING OPPORTUNITIES

One key to being able to see opportunity, or being able to say "yes," is to be open—to possibility and to learning or expanding your experience. If you have a road map for your future, say a 5- or even 20-year plan, where are the gaps in knowledge, experience, or leadership traits? What do you need to do in order to reach interim milestones to follow your path? If you want to be a certain type of leader as a CEO, and you don't start building that toolbox years in advance, then you won't be able to get there. If you aren't sure where you want to go, for instance, if you don't know if you want to be a professional engineer, you cannot get your license if you don't take certain exams. So you can set yourself up for options in the future when they come up, or you can decide where you want your path to go.

Keep an open mind, an open heart, and open ears. Opportunity can come in the smallest and most unexpected ways.

Heather Bennett-Kelley is Project Manager/Engineer at ACCO Engineered Systems, and the 2021–2022 International Emerging Leaders Chair. She has been an ISPE member since 2007.

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INTEGRATING KNOWLEDGE MANAGEMENT and Quality Risk Management

By Martin J. Lipa, PhD, Valerie Mulholland, and Anne Greene, PhD

ISPE held an Expert Xchange on 18 January 2022 entitled "Risk-Based Decision Making: Advancing the Integration of Quality Risk Management (QRM) and Knowledge Management (KM)." The session included presentations and interactive exercises that generated new and useful insights into the current effectiveness of the knowledge that flows into QRM and how a knowledge map can be used to diagnose opportunities to improve KM. The exercises also helped identify the types of knowledge generated during QRM. These insights demonstrated the opportunity to improve risk-based decision-making (RBDM) by uniting risk and knowledge through a suitable framework such as the Risk-Knowledge Infinity (RKI) Cycle.

The session was facilitated by the Pharmaceutical Regulatory Science Team (PRST) in Technical University (TU) Dublin, which presented introductory material to highlight the emphasis on knowledge and KM in the draft International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) ICH Q9(R1) guideline [1]. An introduction to the RKI Cycle and considerations for RBDM in the pharmaceutical quality system (PQS) followed. Interactive exercises explored the knowledge inputs to QRM and the knowledge generated during QRM activities.

This article provides a summary of the presentations and concepts introduced in the session, data gathered during the session, and a preliminary analysis of these data. The genesis of the session was based on work by the PRST in TU Dublin, who identified through research studies the need to intentionally connect QRM and KM as united enablers of the PQS envisioned by ICH Q10 [2].

Benefits to connecting QRM and KM include supporting the primary objectives of ICH Q10, including achieving product realization, establishing and maintaining a state of control, and facilitating continual improvement. Additional benefits were identified in a survey of industry and regulatory authorities [3]: risk assessments that are more data-driven; better risk-based decisions; and increased ability to leverage prior knowledge.

In response, the RKI Cycle was developed by PRST researchers as a framework to unite QRM and KM [4, 5]. This framework was previously introduced at an ISPE webinar in May 2021 [6]. Feedback post-seminar sought additional guidance to support operationalization of the framework.

Concurrently, ICH Q9 has been undergoing revision with the aim to provide clearer guidance on several topics, including RBDM. A draft revision of the updated guideline, ICH Q9(R1), has been issued for public review [7]. This draft revision includes proposed new language on RBDM, as well as a significant increase in the expectations for the application of knowledge. It also includes an introduction to the concept of KM. The authors of this article propose that the RKI Cycle may offer benefits to the effectiveness of RBDM, as well as the other revision topics of ICH Q9(R1) [8].

The three-hour session in the ISPE Expert Xchange [9] included 40 participants.

Table 1: Quotes from ICH Q9(R1) relating knowledge and KM to QRM and RBDM.

Section	Reference in draft ICH Q9(R1) text (emphasis in bold added by the authors)
Introduction	"In the development phase, quality risk management is part of building knowledge and understanding risk scenarios, so that appropriate risk control can be decided upon during technology transfer, for use during the commercial manufacturing phase. **In this context, knowledge is used to make informed risk-based decisions, trigger re-evaluations, and stimulate continual improvements."**
Section 4.3, Subjectivity in QRM	"While subjectivity cannot be completely eliminated from quality risk management activities, it may be controlled by addressing bias, the proper use of quality risk management tools, and **maximising the use of relevant data and sources of knowledge.**" **"Decision makers should… assure** that a quality risk management process is defined, deployed and reviewed and **that adequate resources and knowledge are available."**
Section 5.1, Formality in QRM	"The term **'uncertainty'** in quality risk management means lack of **knowledge about risks.** The level of uncertainty that is associated with the area being risk assessed informs how much formality may be required to manage potential risks. Systematic approaches for acquiring, analysing, storing and disseminating scientific information are **essential for generating knowledge, which in turn informs all quality risk management activities.** Uncertainty may be reduced via **effective knowledge management,** which enables accumulated and new information (both internal and external) **to be used to support risk-based decisions** throughout the lifecycle." "Regardless of how much formality is applied, **the robust management of risk** is the goal of the process. This **should be based on evidence, science and knowledge,** where risk scores, ratings or assessments are supported by data or by an appropriate justification or rationale."
Section 5.2 regarding Risk-Based Decision Making	"Approaches to risk-based decision-making are beneficial, because they address uncertainty through the use of knowledge, facilitating informed decisions by regulators and the pharmaceutical industry in a multitude of areas, including when allocating resources. They also help recognize where uncertainty remains, so that appropriate risk controls (including improved detectability) may be identified to enhance understanding of those variables and further reduce the level of uncertainty." **"As all decision making relies on the use of knowledge, see ICH Q10 for guidance in relation to Knowledge Management.** It is important also to ensure the integrity of the data that are used for risk-based decision making."
Chapter 6 on Product Availability Risks	**"An effective pharmaceutical quality system** drives both supply chain robustness and sustainable GMP compliance. It also **uses quality risk management and knowledge management to provide an early warning system** that supports effective oversight and response to evolving quality/manufacturing risks from the pharmaceutical company or its external partners." "Approval and oversight of outsourced activities and material suppliers is informed by risk assessments, effective knowledge management, and an effective monitoring strategy for supply chain partner performance."
Chapter 7, definition of Risk-Based Decision Making	**"Risk-based Decision Making:** An approach or process **that considers knowledge about risks** relevant to the decision and whether risks are at an acceptable level."
Annex II.9 on the application of QRM to Supply Chain Control	"With regard to product availability risks related to quality/manufacturing issues, **life cycle oversight of the supply chain includes maintaining current knowledge of quality/manufacturing hazards and prioritizing efforts to manage such risks.** Understanding hazards to quality/manufacturing is critical to maintaining supply predictability. When risks are well understood and minimized, a higher confidence in product availability can be attained."

KNOWLEDGE AND KM IN THE DRAFT ICH Q9(R1)

Kevin O'Donnell of the Health Products Regulatory Authority (HPRA, Ireland) and Rapporteur of ICH Q9(R1) presented on knowledge and KM concepts in the draft ICH Q9(R1) guidance [7] that highlight the relationship between knowledge, risk, and RBDM. The theme of O'Donnell's presentation was that knowledge informs decisions about risk, which is a key concept in the draft ICH Q9(R1).

O'Donnell noted this statement in the published ICH Informational Presentation on the revision [10]: "The cross-references to ICH Q10 [in relation to KM] serve to highlight the importance of using available sources of knowledge … and Knowledge Management in general during QRM activities."

Notably, there are 23 references to the word "knowledge" in the draft ICH Q9(R1) guideline [1], and another 3 references to "knowledge management." In the initial version of ICH Q9 released in 2005 [11], there are only 11 references to "knowledge" and none to "knowledge management." This increased frequency of reference to the terms in the draft ICH Q9(R1) guideline adds significant presence to the concepts of knowledge and KM.

AN INTRODUCTION TO THE RKI CYCLE

Martin Lipa, Pharmaceutical Regulatory Science Researcher with the PRST, presented "An Introduction to the RKI Cycle, Rethinking the Connection Between QRM and KM," which highlighted the purpose of QRM and KM as dual PQS enablers. Lipa noted that

Figure 1: The RKI Cycle [4]. (Used with permission. © 2020 Lipa & O'Donnell. All rights reserved.)

Figure 2: The RKI Cycle applied to ICH Q10 [4]. (Used with permission. © 2020 Lipa & O'Donnell. All rights reserved.)

knowledge and risk have an inverse relationship such that the more one knows and understands, the less uncertainty there is, and this presents an opportunity for risk reduction. Lipa introduced a framework linking risk and knowledge, the RKI Cycle, as depicted in Figure 1 [4].

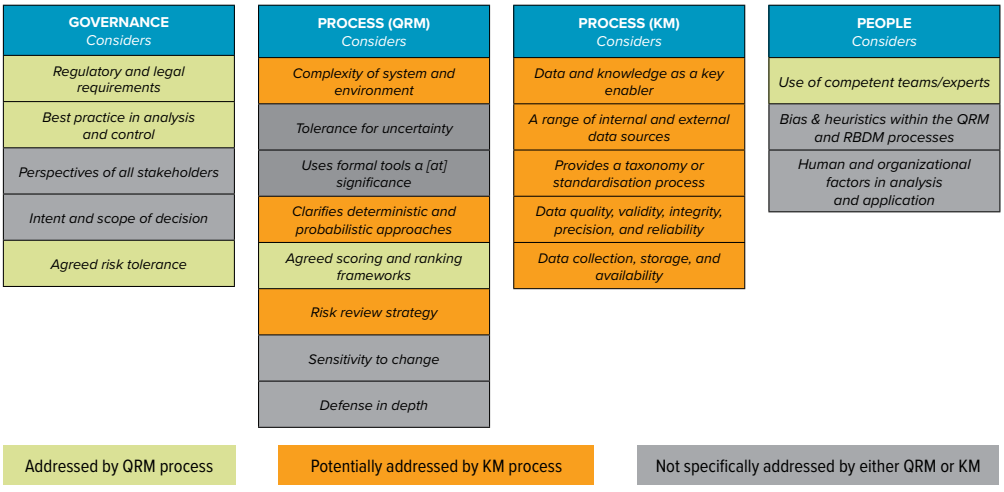
The RKI Cycle is based on the following key concepts:

- Knowledge is both an input to and an output from risk management.
- Knowledge has an inverse relationship with risk (for the purpose of these concepts, risk is used to describe collective actions associated with risk including risk analysis, control, communication, decisions).
- The concept of flow; knowledge flows effortlessly and on demand to inform risk, and risk informs new knowledge.
- The cycle is continuous and perpetual; knowledge is always evolving and should be continually applied to inform risk.
- The cycle applies across the product life cycle.

Lipa then described how the RKI Cycle could be applied to ICH Q10 [2], by relating risk management and KM through a series of six steps (or "nodes") on the cycle, as depicted in Figure 2.

Lipa concluded by sharing research findings that reported 90% of a targeted population composed of industry, regulator, and academia experts surveyed (n = 32) agreed that deploying such a framework would improve QRM/KM integration, resulting in the benefits of more data-driven risk assessments, better risk-based decisions, and increased ability to leverage prior knowledge [3].

Figure 3: Characteristics of RBDM from HROs [13]. (Used with permission. © 2021 Mulholland & Greene. All rights reserved.)



THE ROLE OF QRM IN RBDM

Valerie Mulholland, Pharmaceutical Regulatory Science Researcher with the PRST, shared her perspectives in "Effective Risk-Based Decision Making in the PQS–The Next Horizon in QRM." Mulholland cited the ICH Q9(R1) concept paper [7], noting its acknowledgment that "while there are references in ICH Q9 to decision-making, there is a lack of clarity on what good risk-based decision making actually means, how QRM may improve decision-making, or how risk-based decisions might be achieved." In addition, "…there is a breadth of peer-reviewed research in this area, but the level of visibility (and uptake) of that research within the pharmaceutical industry may be improved."

Mulholland explored the concept of RBDM in the draft ICH Q9(R1) guideline [7], which defines RBDM as "An approach or process that considers knowledge about risks relevant to the decision and whether risks are at an acceptable level."

Mulholland discussed the concept of formality, one of four primary revision topics of ICH Q9(R1) [7], in relation to RBDM. Potential criteria for improved formality in decision-making criteria, based on learnings from NASA, could include complexity, uncertainty, high-stake situations, multiple objectives, and diverse stakeholders [12]. Mulholland suggested multiple potential methodologies and tools for both low-formality and high-formality scenarios, noting that while ICH Q9(R1) refers to formality, it does not provide guidance as to methodologies or tools that could be used.

Mulholland shared the results from a poll conducted at the opening of the Expert Xchange session, which asked participants whether they had a formal definition for RBDM in their PQS. Only 19% indicated they have a formal definition, 38% said there is no formal definition, and 44% reported they are not sure or do not know.

Participants were asked whether their organizations have formal procedures or tools to support RBDM in their PQS: 14% reported no formal tools for RBDM, 63% indicated they had some formal tools adequate for low-complexity RBDM, and 23% reported they had tools adequate for high-complexity RBDM.

The presentation then introduced additional insights, including recently published research examining the definition and characteristics of RBDM from a variety of high-reliability organizations (HROs), which resulted in identifying 21 characteristics of RBDM [13], as illustrated in Figure 3.

Of the 21 characteristics, only 5 are commonly addressed by QRM processes, whereas up to 8 additional characteristics could be addressed with KM processes.

Mulholland concluded by recognizing the role of knowledge in decision-making, whether it be for complex scenarios or more predictable and rule-based situations. Furthermore, it was suggested that effective RBDM is often based on the use of effective QRM and KM, and that decision-makers need to fully understand complexity and uncertainty when making important decisions with respect to risk.

EXPLORING RKI CYCLE NODE I

Node 1 of the RKI Cycle is premised on the assumption that "best available knowledge flows into QRM." The presenters noted that an array of guidance, including ICH Q8(R2), Q9, and Q10 [14, 11, 2], and World Health Organization guidelines on QRM [15], establishes a clear expectation that knowledge informs risk and should be used together to inform decision-making in order to protect the patient. The presenters suggested that at the outset of a quality risk assessment (QRA) exercise, one must be able to answer three fundamental questions:

1. What could go wrong?
2. How likely is it to happen?
3. If it does happen, will you be able to detect it?

Figure 4: Potential information and knowledge inputs into QRM for a commissioning and qualification scenario (not exhaustive) [18].

Regulatory Requirements	PQS Knowledge	Project Capability	QRM Knowledge
• Applicable legislation, laws, environmental health and safety (EHS), etc. • Guidance/best practice documents • Pharmacopeial and test standards • Submitted/approved regulatory filings	• Change management strategy • PQS procedures – process under analysis • Quality records • Maintenance records • Validation procedures and policies • Supplier management/procurement policies and procedures • CAPA data – complaints/audits/deviations/trends • Annual product review (APR) management reviews • Business strategy/priority for product	• Contracts/scope/turn-over-packages • Commissioning and qualification (C&Q) plans/schedules • Capabilities and resources • Laboratory support capabilities • Training procedures and policies • Good engineering practice • Roles and responsibilities • EHS documents – safety data • Conflicting objectives/requirements • KM outputs (legacy requirements)	• Risk management knowledge • Risk management procedures and policies • Defined risk question/scope • Trained risk management practitioners/facilitators • Specify a timeline, deliverables, and appropriate level of decision-making for the risk management process

Product Knowledge	Process Knowledge	
• Life cycle documents • Specs/acceptance criteria – product • Specs/acceptance criteria – materials • Design/validation documents – measurement and analysis systems • History of product issues (product under analysis or related) • Supply chain (product and materials) • Toxicology data/acceptable daily exposure (ADE) value • Information and/or data on the potential hazard, harm, or human health impact relevant to the risk assessment • Degradation pathways/stability data	• Process user requirements • Specifications/acceptance criteria – process • Design/validation documents • Facility and utilities • Process and equipment • Process controls • Measurement and analysis systems • Software systems • Cleaning • History of problems with process/outputs • Drawings • Calibration requirements	• QRM documents from design/previous stages • System integration requirements • Equipment manuals/technical specifications • Materials of construction • Process capability/performance indices • Routes for contamination/cross contamination • Cleaning process performance capability • Training and competence in process • Prior knowledge/lessons learned – current or other locations

In addition, based on practices beyond the pharmaceutical industry [16], a fourth question was posed:

4. How sure are you [of the answers to 1–3]? How sure do you need to be? Is the result suitable?

Linking to the intent of node 1 to apply the "best knowledge to QRM," the presenters posed these questions:

1. How will you ensure you apply the best knowledge, experience, know-how, expertise, and prior knowledge to perform an optimal risk assessment and support the best possible risk-based decision?
2. Is the most current knowledge visible, available, and accessible on demand?
3. Is the knowledge of sufficient quality for use?
4. What are you missing?

The presenters then introduced the concept of knowledge mapping [5, 17] as a means to help answer these questions and address the intent of node 1.

KNOWLEDGE INPUTS TO QRM

A key input to a knowledge map is understanding the knowledge inputs to a process. For example, taking a typical commissioning and qualification scenario, the authors identified potential sources of knowledge to support the associated QRM (and consequentially RBDM) [18]. The facilitators compiled the knowledge inputs identified from these sources into an aggregated list, representing 57 potential inputs from 9 guidelines. These were assigned into six categories and are shown in Figure 4. Although not a fully definitive or exhaustive review, given the scope and relevance of the guidance documents reviewed, the facilitators propose this

list represents a significant portion of the information and knowledge inputs to the QRM process.

Exercise 1: Knowledge Map Case Study

As an illustration, the presenters introduced a knowledge mapping case study for the installation of an autoclave. Most (52) of the aggregated list of 57 knowledge inputs in Figure 4 were considered relevant to the risk assessment of an autoclave installation. A subset of these inputs was selected to illustrate the knowledge mapping process.

The instructions for knowledge mapping were introduced using a simplified knowledge map template [18], which assessed knowledge type (explicit or tacit), knowledge flow, and knowledge quality.

Explicit knowledge was defined as codified knowledge (i.e., something written down in a document, a video, or an image), whereas tacit knowledge was defined as the knowledge in people's heads (i.e., know-how, experience, expertise).

Knowledge flow was defined as to whether the knowledge was available and accessible on demand. Knowledge quality was defined as the knowledge being reliable for intended use, having sufficient context and rationale, and being complete and accurate [18]. Qualitative descriptions were provided for each of three levels of flow and quality, ranging from poor to marginal to excellent.

The facilitators presented an example and mapped five knowledge inputs, covering both types of explicit and tacit knowledge. The first three knowledge inputs were mapped using an interactive poll designed to solicit perspectives from the participants to illustrate the current state of process knowledge on design and validation documents for facilities and utilities; prior knowledge/lessons learned from attendees or other sites; and routes for contamination/contamination control.

Two additional inputs were mapped in the session through an exchange of dialogue between facilitators (Mulholland as QRM expert and Lipa as KM expert), designed to illustrate to the participants the deeper thinking and discussions that should occur during a knowledge mapping exercise. These inputs were product/process knowledge; QRM documents from product/process development; and process knowledge: system integration requirements (e.g., manufacturing execution systems, electronic batch records, building management system).

Knowledge Map Results and Key Insights

Almost all attendees provided responses for the first three knowledge inputs. Although the sample size was small, the results are in line with Lipa's previous experience. The authors propose the following insights:

- The flow and quality of explicit knowledge are markedly higher than that of tacit knowledge.
- Although results for explicit knowledge flow and quality fared better than that of tacit knowledge, there is clearly an opportunity for improvement, as on average just over half of respondents rated flow and quality as excellent, with a substantial percentage rated as only marginal or poor.
- Tacit knowledge flow received the lowest ratings, suggesting this may be an area for focus and improvement.
- Participants rated communication and lessons learned between sites as poor.
- There was a concerning marginal/poor rating of both tacit and explicit knowledge flow and quality, given the process importance of the equipment application and its role in the contamination control strategy, suggesting that even for critical processes, there may be gaps in information quality and reliability.

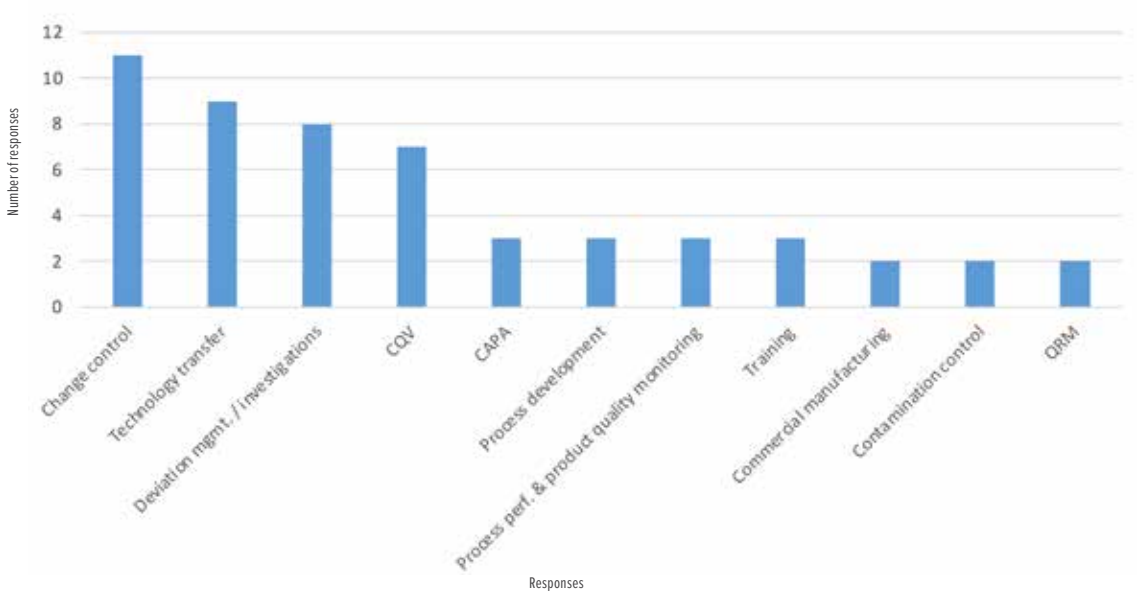
Knowledge Mapping: Potential Value for QRM

At the completion of the activity, the participants were asked to reflect on the utility of knowledge mapping as demonstrated through the case study exercise. They were asked the following questions via a survey about knowledge mapping.

In response to the first question, "Does knowledge mapping help you think more expansively about QRM knowledge?," 97% of participants agreed or strongly agreed that it does.

Additional responses to other questions suggest that knowledge mapping has a significant potential utility in supporting QRM: 93% agreed that knowledge mapping can help recognize gaps in explicit knowledge; 86% agreed that knowledge mapping can help recognize gaps in tacit knowledge; 83% agreed that knowledge mapping can be used as a template or checklist to

Figure 5: Additional applications for knowledge mapping.



support QRM; and 97% agreed that knowledge mapping can highlight opportunities to improve KM.

Finally, the participants were asked what other three applications (e.g., processes) might benefit from knowledge mapping. Figure 5 suggests recognition of the opportunity for knowledge mapping to benefit change control, technology transfer, deviation management and investigations, and CQV (commissioning, qualification, and validation). This demonstrates other areas of opportunity and potential further study.

Figure 5 shows an additional seven processes that could benefit from knowledge mapping. In addition, the following applications/processes received one vote each from participants during the survey, identifying additional opportunities:

- Assessing standard operating procedures
- Audit program
- Continuous improvement
- Continued process verification
- Data analysis
- Environmental monitoring
- Gaps in subject matter expert knowledge
- Global supply chain
- IT compliance
- New equipment/laboratory project
- New facility design
- Post-market surveillance
- Product teams that share knowledge across multiple sites

Exploring RKI Cycle Node 4

Node 4 of the RKI Cycle is labeled "acquire, grow, capture and retain new knowledge" (see Figure 2). The scope of this knowledge is not exclusive to QRM knowledge; node 4 is the primary injection point of product and process knowledge because it is acquired during development and commercial manufacturing from many diverse processes.

The focus for this workshop was primarily the knowledge generated by the QRM process to explore what knowledge is generated (node 3) and how it flows into KM (node 4). Recognizing the RKI Cycle is a continuum connecting knowledge and risk, the analysis of node 4 is tightly linked to node 3. Node 3 represents the generation of the knowledge from the QRM processes (i.e., new knowledge from QRM and "what has one learned"), whereas node 4 is the intake of this knowledge into KM (i.e., as a means to ensure this knowledge is available in the future to those that need it).

Knowledge as an Output from QRM

In regulatory guidance, it is evident that knowledge is an expected output from QRM, both from the QRM process activities (e.g., risk assessment results) and the knowledge created as a result of the risk management process (e.g., additional studies). For instance, ICH Q8(R2) [14] says pharmaceutical development "provides an opportunity to present the knowledge gained during application of scientific approaches and QRM." It also states, "appropriate use of QRM principles can be helpful in prioritising the additional pharmaceutical development studies to collect such knowledge."

WHO Guidelines on Quality Risk Management–Annex 2 [15] says that "the QRM approach may be used to…facilitate the transfer of process knowledge and product development history to ease product progression throughout its life-cycle and to supplement already available knowledge about the product." Also, "early in development, the purpose of the QRM process may be to acquire sufficient product and process knowledge to assess risks associated with [the process]." The WHO Guidelines also say,

"a crucial aspect of product development and QRM is the maintenance of an effective and secure knowledge management and documentation system."

KM Process Model

The presenters provided a simplified version of the KM process model (Figure 6) [4] to introduce the participants to the model and the underlying intent that KM is intended to enable knowledge to flow to the right person, at the right time, to inform the best decision.

The KM process model illustrates that many processes—inclusive of QRM—generate knowledge that should flow into KM, and subsequently use (apply) knowledge available through KM—also inclusive of QRM. The authors believe that herein lies the opportunity regarding QRM knowledge flowing in through node 4: How this knowledge can be captured and made available for the future to better inform the next risk assessment, to optimize risk controls, and to enhance risk communications—all to support RBDM and the opportunity to minimize the risk of harm to the patient.

Exercise 2: Exploring Knowledge Generated During QRM

The authors believe that current QRM activities typically focus heavily on risk assessment (as part of node 2). Although risk control, risk communication, and risk review are also part of the QRM process, these activities should evolve and be enhanced as knowledge grows, and the RKI Cycle provides a methodology to ensure this. In addition, the recurrent nature of the RKI Cycle also promotes a reevaluation of the risk assessment as knowledge grows [19].

Exercise 2 was designed to explore this premise with a view to informing future research, while also providing a networking opportunity for the participants. To this end, the facilitators set up three breakout topics for six teams (two teams per topic). The participants were asked to answer the following questions:

1. What knowledge is created during a QRM exercise?
2. What is the role of KM in risk review?
3. What is the role of KM in risk communication?

The feedback from the participants is summarized in the following sections and will inform ongoing research on the operationalization of node 4.

What knowledge is created during QRM activities?

Table 2 presents the combined output from the two teams assigned to this question. The responses are unaltered quotations from participants, aside from removing duplication, making grammatical edits, and grouping related remarks.

The breakout teams also shared the following comments:

- "Knowledge mapping process can also highlight where the weaknesses might lie within business processes."
- "A risk that it is more difficult to actually digest all this 'new' information [explored during quality risk assessment (QRA)] and communicate it effectively."
- "The issue of confidentiality of this information can be a key issue. Making it visible and accessible can be a problem. Need to be careful about the level of availability/liability issues of data/knowledge that has not been reviewed by the 'sponsor.'"
- "Also need to consider what might be available for auditors and inspectors to review [of the additional knowledge captured during QRA]."
- "Are we good at disseminating these details in QRM documents (QRM tools/meeting minutes)? Maybe good at flow/dissemination but doesn't always meet the knowledge quality criteria in the knowledge transfer; not always good at sharing this. Sometimes the context and 'metadata' about the issue under review is not embedded in the knowledge capture, makes it difficult to reuse."

Figure 6: KM process model. (Used with permission. © 2020 Lipa & O'Donnell. All rights reserved.)

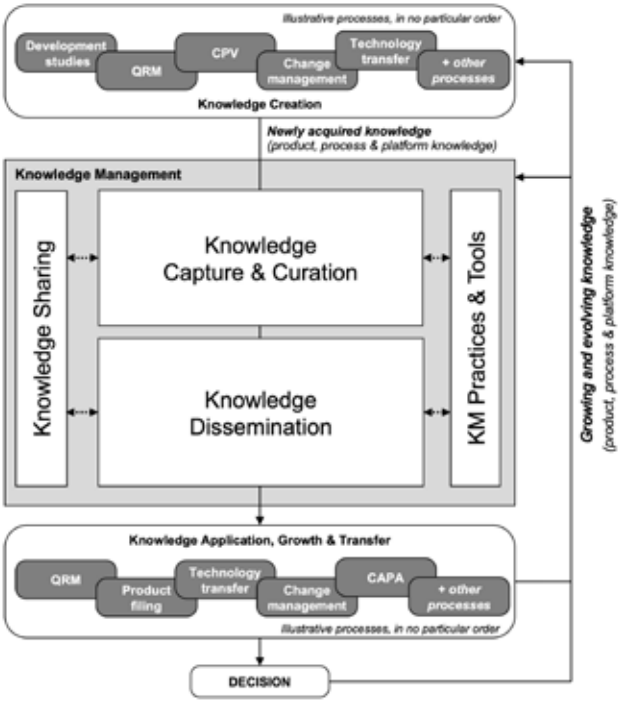


Table 2: Breakout summary: Knowledge created during QRM activities.

"Explicit knowledge through identifying studies that may need to take place to inform rating decisions."
"Transforming tacit into explicit knowledge—documenting for the first time some tacit knowledge from SMEs."
"Knowledge to inform stakeholders/decision-makers/senior management, informing investigations, strategies."
"Life-cycle knowledge/system health; keeping knowledge contemporary."
"Information to be leverage for new product introduction; predictive analysis."
"Gaps in control strategies; gaps in knowledge that become substrate for further study."
"Knowledge to better understand the compliance and supply chain risks."

What is the role of KM in risk review?

Table 3 presents the combined output from the two teams assigned to this question.

Table 3: Breakout summary: The role of KM in risk review.

"KM to risk review–similar devices and production CAPAs."
"PPQ – annual product review to capture KM to feed into QRA."
"Answer is dependent on the question you ask?"
"QRM is built in PQS. Risk review happens in change control, new product introduction, etc. Periodic risk review is codified in a formal SOP for some of the attendees but not all. Formal and informal tools are used for risk review. There are many challenges with risk review, keeping the risk assessment living, updating regulatory submissions where needed. Risk review is still immature in most companies because of historical knowledge of system and processes lies with the individual and is not well-documented."

What is the role of KM in risk communication?

Table 4 presents the combined output from the two teams assigned to this question. The responses are unaltered, aside from removing duplication, making grammatical edits, and grouping related remarks.

Table 4: Breakout summary: The role of KM in risk communication.

"Challenge: Getting the decision-maker(s) get enough information to justify the decision without being too much."
"For explicit knowledge you build systems to know where [to find] things (you want to make sure you have the right system to get the right data you need); the longer you need the explicit knowledge, the more formal it should be so you have additional context and rationale."
"Tacit knowledge is difficult: hard to put everyone's brain into system (key area of opportunity?)."
"Instances where companies are hurting because the experts have left: Don't just document the results but the rationale. A process map is very helpful."
"Using lessons learned—there is a lack of using this; you do a lessons learned at the end of the process, but no one looks for the lessons when you start a new project (this was a highly agreed discussion!)."
"With CROs there is so much turnover (even in the middle of a study) and that impacts the ability to capture the lessons as well as prior history of the study."
"KM facilitates the sharing of key data and ensure visibility and relationship to risk."
"KM provides awareness of the level of risk and the consequences of the risks."
"KM provides another knowledge source document that can be referred to and facilitates informed decisions."
"KM focuses the KM group's attention to high-risk gaps, where the knowledge needs to be accessible, where the knowledge can be located."
"Risk communication needs to understand the audience and stakeholders and their knowledge."
"KM provides a framework for risk communication."
"KM summarizes the site's knowledge communicating risk."

CONCLUSION

There are substantial benefits, and an emerging expectation, in using knowledge to inform risk management and RBDM. Both the RKI Cycle and KM can play a major role in providing the best knowledge to make the best decision in the interest of the patient. Tables 5 and 6 summarize the insights gained during the two exercises.

Table 5: Summary of insights for exercise 1 (RKI Cycle node 1).

Examining industry and regulatory guidance reveals many types of knowledge relevant to risk assessment.
A knowledge map of the knowledge inputs to QRM suggests: • A significant opportunity to better manage the flow and quality of explicit knowledge to better inform QRM • A significant opportunity to better manage the flow and quality of tacit knowledge to better inform QRM • Requirements for KM can be informed through insights gained during knowledge mapping
There was strong agreement that knowledge mapping can help one think more expansively about QRM knowledge.
Knowledge mapping has potentially a high degree of utility for QRM, with agreement that knowledge mapping can better recognize gaps in explicit knowledge and tacit knowledge, can be used as a job aid or checklist to support QRM, and can highlight opportunities to improve KM.
Many additional opportunities for knowledge mapping were identified by the participants, led by the opportunities of change control, technology transfer, deviation management/ investigations, and CQV.

Table 6: Summary of insights for exercise 2 (RKI Cycle node 4).

Knowledge is an output from QRM.
Diverse knowledge is created during QRM activities, including explicit and tacit knowledge, which informs future studies, helps others understand the past, and helps inform decision-makers. Such a knowledge mapping process can also be helpful to highlight where weakness may lie in a business process.
KM can benefit risk review through linking to knowledge on similar products, devices, CAPAs, current manufacturing, SMEs, historical knowledge, etc.
KM can benefit risk communication by informing decision-makers, protecting tacit knowledge from employee turnover, sharing data and relationship to risk, increasing awareness of the level of risk and consequence of risks, helping focus attention on high-risk gaps where knowledge needs to be accessible, and providing a framework for risk communication.
KM contributes to transparency and evidence-based QRM and RBDM.

Taken in aggregate, these insights confirm the potential for the RKI Cycle to be an integral part of the solution in better uniting risk and knowledge to lead to more effective RBDM. The exercises during the session, in particular the knowledge mapping exercise associated with node 1, provide tangible means as to how the RKI Cycle can be operationalized in support of RBDM. Exercise 2 will inform ongoing research for the operationalization of node 4.

This session also revealed the opportunity for several potential next steps, including building awareness of and competency in knowledge mapping, extending knowledge mapping to additional applications (e.g., change management, technology transfer), the opportunity to improve risk communication and risk review through KM practices, and continued definition of steps to further operationalize the RKI Cycle.

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FROM DATA TO KNOWLEDGE MANAGEMENT: What to Consider

By Melanie J. Adams, Paige E. Kane, PhD, CPIP, and Anne Greene, PhD

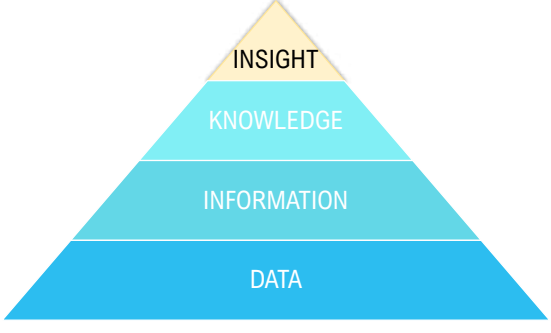
Although data and knowledge are both stand-alone disciplines that need to be systematically managed, they also must have a connection. Understanding the relationship between data and knowledge management processes and how people are leveraging advances like Pharma 4.0™ combined with these processes enables quality data transition to knowledge that can help pharmaceutical companies. The authors also want to generate understanding on how using the knowledge acquired by people through experience (tacit knowledge) can further connect both data and knowledge management systems, yield positive strategic results, and deliver more efficient processes within organizations.

Knowledge management (KM) is a stand-alone discipline; however, it has relationships with other disciplines. This article explores the relationship between data and knowledge, a deeper look that follows up on the Pharmaceutical Knowledge Ecosystem [1], which looks at how the pharmaceutical industry acquires data, transforms this data into tangible knowledge, and derives valuable insights throughout the process.

The origin of this ecosystem builds upon the data, information, knowledge, and wisdom (DIKW) hierarchy [2]. Over time, this theory has been developed, and was published in 2018 replacing *wisdom* with *insights*, as shown in Figure 1.

Kane reported that wisdom is widely agreed to be a "uniquely human" characteristic, whereas insights take into account current technological advances and allow data transformation to lead to insights. Although insights may be derived by people with knowledge and experience, they may also be derived from computing or machine-learning models that identify trends and correlations previously not possible to see from experience alone.

Figure 1: DIKW hierarchy, as adapted by Kane [3].



Following on from that: Although it is useful to replace wisdom with insights in the DIKW hierarchy, on reflection, Lipa [4] proposed that the goal is to achieve understanding. Insights could be regarded as discrete events, whereas understanding represents a holistic comprehension: a state of mastery of a given domain or topic. This state of mastery could manifest, for example, as a mechanistic understanding of a complex chemical reaction or as an accurate predictive model for the relationship between process parameters and their impact on final product quality attributes. In each example, there is a progression from being naïve to developing

understanding (i.e., a state of mastery) based on accumulated data, information, knowledge, and insights, as depicted in Figure 2 [4].

Mastering the progression of data to information to knowledge to insights and understanding (DIKIU) presents the opportunity to be able to make informed and effective decisions based on accumulated evidence, as provided by the underlying structure.

DATA VERSUS KNOWLEDGE

In everyday conversations, it is not unusual to hear the words *data* and *knowledge* used interchangeably. This section offers definitions and descriptions of these terms.

The Cambridge Dictionary defines data as "information, especially facts or numbers, collected to be examined and considered and used to help decision making, or information in an electronic form that can be stored and used by a computer" [5]. It defines knowledge as "understanding of or information about a subject that you get by experience or study, either known by one person or by people generally" [5].

The definition of data emphasizes information in its raw form, without context. It is context and understanding that increases data's usefulness and transforms it into knowledge.

From the definitions of data and knowledge, it is clear that having information or understanding about a subject is gained through experience. It should be noted that experience is known or gained by people.

MANAGING DATA AND KNOWLEDGE

Managing Data

Transferring data to knowledge does not typically happen organically. Procedures that enable users to derive value (e.g., lead to decision-making or insights) from an organization's data or knowledge base should be in place to ensure the information can be validated and trusted. To do this, there should be several procedures in place.

The ISPE *GAMP RDI Good Practice Guide: Data Integrity by Design* has described managing data as a life-cycle process with five phases [6]. The key points in the life cycle are:

- Creation
- Processing
- Review, reporting, and use
- Retention and retrieval
- Destruction

The authors of this article would like to highlight and include two further important activities and processes for managing data to this list within Table 1: data governance and data integrity.

Table 1 highlights examples of data-related processes and why they are important.

Managing Knowledge

As with other management disciplines, definitions for KM are plentiful. In this article and in alignment with pharmaceutical industry related literature, two definitions are highlighted:

Figure 2: DIKW hierarchy, as adapted by Lipa [4].

Table 1: Data-related processes.

Process	Reason for Importance
Data governance	Governance refers to what decisions must be made to ensure effective management and use of IT (decision domains) and who makes the decisions (locus of accountability for decision-making) [7].
Creation: data creation and collection	Many different data sources exist; generally the use of spreadsheets is widespread, and some data is available in handwritten notes, lab notebooks, and printouts from stand-alone devices. These manual notes and printed data sheets are manually transcribed into electronic format. There does exist a more sophisticated case where data is stored in commercially available databases such as laboratory information management systems (LIMS) or in-house systems set up by organizations themselves [8].
Processing: data analysis and processing	The main purpose of collecting and analyzing data in commercial manufacturing is to set up a product and process control environment. Raw data is given context by adding information and explaining what the data means, thus presenting information in a required format.
Retention and retrieval: data retention and retrieval	In routine manufacturing, manufacturing execution systems (MES) control and document the manufacturing processes. For analytical measurement results, LIMS systems are often used along with Excel spreadsheets. In the case of Excel spreadsheets, GMP validation is possible. Manual extraction of data from paper-based batch records is another option [8].
Review, reporting, and use: data storage, dissemination, reporting, and use	Once generated, the data and information require long-term storage and simple reuse options. KM tools organize the acquisition, storage, and dissemination of the product knowledge.
Destruction: data destruction	Ensure the correct original data is disposed of after the required retention period [6].
Data integrity	Product data should ensure end-to-end traceability and data integrity in order to release a batch. It is expected that the integrity of pharmaceutical data assets should be compliant with attributable, legible, contemporaneous, original, and accurate (ALCOA) principles [9].

KM processes can assist in ensuring knowledge is shared in the form it is required for the end user and it is communicated, consistent, and findable.

ICH Q10 defines KM as:

> A systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components. Sources of knowledge include but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and change management activities [10].

American Productivity and Quality Center (APQC) defines KM as:

> The application of a structured process to help information and knowledge flow to the right people at the right time so they can act more efficiently and effectively to find, understand, share, and use knowledge to create value [11].

The ICH definition describes KM with a more narrow perspective than the APQC definition; the APQC definition is more commonly used by KM practitioners because it embraces the two main aspects of KM: The needs of the knowledge user and the needs of managing knowledge within an organization.

Table 2 presents examples of KM processes and tools that enable a systematic approach to knowledge flow and indicating their importance. These KM are discussed in length in the ISPE *Good Practice Guide: Knowledge Management in the Pharmaceutical Industry* [12].

RELATIONSHIP BETWEEN DATA AND KNOWLEDGE

Some challenges in assessing the relationship between data and knowledge include large volumes of information make it difficult to focus on the most important elements; multigenerational preferences in the workplace for consuming information; the concept of data privacy; and demonstration of the KM value proposition, which enables buy-in and sponsorship, embedding the concept of knowledge as an asset [13].

Table 2: KM processes.

Processes and/or Tools	Reason for Importance
KM plan KM maturity assessment	These are required for planning, understanding requirements of the organization, and defining the process [12].
Content management Searching platforms Product knowledge	These relate mostly to explicit-based knowledge: "a declarative type of knowledge that can be readily articulated (in words or images), coded, stored, and accessed" [12]. Explicit knowledge can be learned as facts.
Communities of Practice Lessons learned Tacit knowledge retention	These relate mostly to tacit knowledge: "a context-specific type of knowledge, acquired through personal experience or internalization and would reside within people's minds rather than a physical media or information system. Often referred to as 'know how.'" [12]. Tacit knowledge is gained through experience. It is rarely written down and is hard to capture and validate, but when applied, it increases right first time (RFT) and facilitates continual improvement.
KM roles KM training KM governance	Enablers to the KM process [12].

It is through data analysis and processing that the relationship between data and knowledge becomes evident. To manage the large volumes of information and extract the important elements, the analysis and processing of data has to add value. To focus on what that value is for an organization, define the objective that an organization or a team needs to achieve from the data, perhaps in the format of a problem statement. To solve the problem, one needs to understand what sources of data and information are needed, and in particular what type of analysis is to be carried out. For example:

- Descriptive analysis: Identifies what has already happened.
- Diagnostic analysis: Focuses on understanding why something happened.
- Predictive analysis: Allows one to identify future trends based on historical data.
- Prescriptive analysis: Allows one to make recommendations for the future.

After the sources of data and information needed are identified and the type of analysis determined, the required data should be collected and aggregated. This includes quantitative (numerical) data or qualitative (descriptive) data. In the pharmaceutical sector, several types of data management platforms that automate data collection are used; some examples can be found in Table 1.

The data from these platforms can be considered "clean" (i.e., data that has had errors, duplicates, and unwanted data points removed) because they are validated systems. The data is reported in a structured manner.

It is through the analysis of data that information, knowledge, and insights are gained. These insights should be shared within the

organization with key members who need them. This flow of knowledge is important because raw data will yield no value without knowledge; thus, analysis is needed, which enables insights to be shared in a digestible manner by everyone who receives the information.

Often key decisions are made based on these insights, which have been communicated in the form of reports, dashboards, and interactive visualizations, so they must be clear and unambiguous. Ideally, all data should be shared so decisions are made based on a complete picture, and the final decision is scientifically sound and based on insightful facts. Insights that are open to interpretation should be flagged. Communication is key when sharing this information. KM processes can assist in ensuring knowledge is shared in the form it is required for the end user and it is communicated, consistent, and findable. This is the real function of the Knowledge Ecosystem.

FUTURE CONSIDERATIONS

Pharma 4.0™ [14] proposes that the pharmaceutical industry adopt a standardized approach to the collection, storing, and analyzing of data. It suggests that the pharmaceutical industry needs a system that can span across one organization to remove silos and data isolation, is a user-friendly database, and can interact with other systems (interface). The purpose of this is to avoid data inconsistency. Data itself cannot take any actions other than what it is programmed to do; however, it can be programmed to take actions that could lead to future problems due to inconsistency.

When maximizing the flow of knowledge in an organization, four key factors should be considered to enable a holistic KM program: people, process, content, and technology [13]. All of these factors are required to be successful; if one is missing, knowledge flow will not succeed. People are the primary consumers and generators of knowledge. Technology and content alone will not solve knowledge flow issues. If people are not using the Knowledge Ecosystem, knowledge flow will be poor. People manage processes and understand the content required, keeping in mind as well that people hold the organization's tacit knowledge.

Knowledge is a valuable asset, but often it is not treated that way. Approaches to KM and sometimes data management can vary. This can also result in poor flow of knowledge. Organizations should understand that in the current climate of increasingly complex information generation and large volumes of data, those who manage knowledge well can realize a competitive advantage [13].

CONCLUSION

With the use of technology, a huge amount of data and information can be processed. This ability is growing exponentially;

When maximizing the flow of knowledge in an organization, four key factors should be considered to enable a holistic KM program: people, process, content, and technology.

however, processing through technology solutions is limited to data and explicit knowledge. Although various technologies have been developed to store, organize, and reuse information, tacit knowledge (the human factor) is still needed to integrate and make sense of this information to create value. Through KM processes (capturing explicit knowledge) and communities of practice connecting people (capturing tacit knowledge), explicit and tacit knowledge become available for use. The more subject matter experts (SMEs) connect across the organization, the more powerful decision-making and the resulting actions will become.

Managing organizational data and knowledge should be a process-driven systematic approach with a life cycle so that data, information, and knowledge are proactively and continuously captured, analyzed, stored, and disseminated. A robust and reliable KM ecosystem integrates product and process information and supports the capture of explicit and tacit knowledge.

As pharmaceutical organizations adopt the Pharma 4.0™ philosophy and embrace the huge amount of data, data connections, structured information, and knowledge in repositories, opportunities for more effective decision-making emerge. This will have a profound effect on how business is managed in the future.

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EFFECTIVE KNOWLEDGE MANAGEMENT in Mergers and Acquisitions

By Paige E. Kane, PhD, CPIP

As the pharmaceutical industry continues to grow and evolve, a significant contributor to innovation and evolution is mergers and acquisitions (M&A). M&A can enable academic researchers and small companies to fund and commercialize innovative products. In addition, M&A can help larger organizations secure new and complementary technology and products. In the pharmaceutical industry, knowledge management (KM) has been identified as an enabler to a pharmaceutical quality system (PQS) through the publication of ICH Q10 [1]. This article discusses, at a high level, the potential opportunities of KM contributing to the success of pharmaceutical M&A through end-to-end (E2E) knowledge transfer.

This article draws on the language and understanding of knowledge capture and transfer in the ISPE *Good Practice Guide: Knowledge Management in the Pharmaceutical Industry* published in 2021 [2]. The author acknowledges that, in some environments, the culture may be hostile and as such it could be difficult to integrate KM practices. Notwithstanding this challenge, it is useful to have a thoughtful process to explore the opportunities to capture and transfer knowledge.

KM more broadly entered the discussion in the pharmaceutical industry in 2008, when ICH Q10 Pharmaceutical Quality System was published [1]. In it, KM was identified as one of the two enablers to a PQS. ISPE published the *Good Practice Guide: Knowledge Management* in 2021 not only highlighting KM as a PQS enabler, but also describing business advantages to effectively managing knowledge for operational effectiveness.

It may be easy to think about operational effectiveness through the lens of routine operations. However, less-frequent operations, such as M&A, also pose an opportunity for KM to help ensure the success of the transaction and sustained success thereafter [3]. Merck & Company highlighted the Schering-Plough acquisition in 2009 as one of the key factors in a programmatic approach to KM [4]. A 2020 Pharma Intelligence white paper describes M&A as an essential part of normal business operations, highlighting three key objectives: Accessing external innovation, strategic portfolio management, and delivering on stakeholder returns [5]. Chancellor reported that between 2000 and 2019 there were 596 major (> $100 million) M&A deals. Building on a solid history of M&A in the industry, Fierce Pharma reported that prospects for future M&A are strong as biopharmaceutical companies have $1.7 trillion to spend on M&A in 2022.

Models to describe M&A phases are plentiful, but here are high-level elements where an organization might apply KM tools and approaches to deliver a successful E2E knowledge transfer:

- Preacquisition (prior to public announcement, inclusive of due diligence): Because preacquisition activities are often fluid, and usually confidential, employment of KM tools in the phase is challenging, thus this phase will not be discussed in this article

- Acquisition (activities post announcement needed to get to "Day 1")
- Integration and value capture: 1+ years post transaction

Prior to looking at KM in M&A, it is useful to look at typical types of knowledge. The ISPE KM GPG discusses two types of knowledge: explicit and tacit. Explicit knowledge is knowledge that is captured and codified: such examples can include procedures, manuals, papers, and websites. Tacit knowledge is knowledge that resides in the heads of people—their experiences and know-how. Tacit knowledge is much harder to articulate and capture [2]. Information is contextualized data, which is a form of explicit knowledge. Both tacit and explicit knowledge have been identified as key to competitive advantage by Rahimli [6]. Nonaka, the first Distinguished Drucker Scholar in Residence at the Drucker School and Institute, noted "In an economy where the only certainty is uncertainty, the one sure source of lasting competitive advantage is knowledge" [7].

A key question is: How might one use KM as a competitive advantage during M&A and what KM tools and processes might one use to maximize the effectiveness of knowledge transfer? The following sections explores the opportunities for applying KM to drive effectiveness of knowledge transfer in M&A in three areas:

- Identification of information and knowledge
- Holistic knowledge transfer
- Retention of critical knowledge

Table 1 gives examples of KM tools and approaches that one might consider to employ, for both tacit and explicit knowledge capture for the three areas.

IDENTIFICATION OF INFORMATION AND KNOWLEDGE

During the preacquisition phase of M&A, there is an evaluation of processes, systems, and assets, both physical and intellectual. Many organizations have teams of people that may specialize in evaluations for M&A. One area of opportunity common in other sectors, which the pharmaceutical industry could adopt, is the inclusion of one or more KM subject matter experts (SMEs) on the M&A team; this could be during the due diligence phase and/or the knowledge transfer phase. Examples of companies from other sectors that used KM SMEs for M&A include Schlumberger, AT&T, PTT Exploration and Production, and SNC Lavin, to highlight a few [8].

To assess the landscape prior to knowledge transfer activities, an evaluation of the topical knowledge (e.g., technical knowledge, business processes, R&D elements, etc.), methodologies for storage and retrieval (search) and SMEs should be completed. Due to the scope of the M&A project, it may not be possible to evaluate all processes for knowledge capture, thus a prioritized focus should be developed by the M&A team.

HOLISTIC KNOWLEDGE TRANSFER

When pondering how to optimize knowledge transfer activities for the acquisition, or "Day 1," phase of the merger and acquisition and what knowledge is needed for integration and value capture, one could consider linking the knowledge transfer to the process of technology transfer (TT). TT is a common pharmaceutical product life-cycle element in which technical product knowledge and process knowledge are shared between a sending site and a receiving site.

TT is not only an important knowledge transfer activity, but it can also be a rich source of new knowledge as often a new process is run on new or different equipment or facilities. It is common for organizations to develop a knowledge transfer plan as an element of a TT plan or specific KM TT plan to outline the objectives, timelines, tools, and processes to be used to capture knowledge created and shared during a TT activity.

Linking to the concept of a TT plan, one might consider developing a specific knowledge transfer plan for M&A activities. It may not be possible to capture all topics, but a risk-based approach should be considered when developing such a plan. Additional KM approaches to consider are discussed next.

- Knowledge mapping: This helps organizations understand what knowledge exists in functions and the flow of knowledge through business processes.
- Expertise location: Not all organizations have expertise location systems, but they may be useful to identify SMEs for critical topics.
- Search and taxonomy: Understanding and evaluating technology systems are standard elements of M&A activities; however, the use of common taxonomy and term stores should be evaluated and considered to ensure that any new content/explicit knowledge generated or transferred can be efficiently located in the receiving organization. Systems that effectively use synonyms may enhance search operations as the two organizations' norm on terminology and nomenclature. The ISPE KM GPG proposes taxonomy is a standard metadata that functions as a common language [1].
- After action review (AAR) and lessons learned (LL): AAR is a powerful KM process that provides a framework to reflect and learn. Since 1989, the US Army has used AAR and broadly publishes these reviews for public use [9, 10]. Many organizations use this approach as a starting point but keep it simple, asking several successive

Table 1: Examples of KM tools and approaches.

KM Tool/Approach	Explicit	Tacit
Knowledge mapping–Functional knowledge	X	
Knowledge mapping–Business process knowledge	X	X
Taxonomy and search	X	
Expertise location		X
After action review/lessons learned (AAR/LL)		X
Communities of Practice (CoPs)	X	
Knowledge transfer plan (KT plan)	X	X
Retention of critical knowledge (ROCK)		X

How might one use KM as a competitive advantage during M&A and what KM tools and processes might one use to maximize the effectiveness of knowledge transfer?

questions such as: what was supposed to happen, what actually happened, what went well, what did not go well, and who needs to know. These simple questions set the foundation for lessons to be incorporated into future activities. AAR/LL is a powerful knowledge capture tool with a specific focus on capturing tacit knowledge.

- Communities of Practice (CoPs): These groups of people collaborate for a purpose and aim to connect around a common topic. CoPs topics can be technical (engineering, scientific) or business (project management, operational excellence, etc.). Quick wins for new people joining an organization via M&A activities can be achieved by connecting new colleagues to CoPs in their area of focus. The ability to connect with fellow practitioners can immediately extend their network to gain help and information and to share learnings that may be valuable to their new organization.

An additional area of consideration to aid in knowledge transfer is a review of the information technology (IT) systems of the respective organizations. Interoperability, or the ability for systems to seamlessly exchange and use data and information, is a key consideration of not only data transfer, but also the explicit knowledge to ensure content and document visibility and availability.

RETENTION OF CRITICAL KNOWLEDGE

Retention of critical knowledge (ROCK) is key during normal operations but even more important during M&A. KM tools and processes, by design, are intended to enable accessibility and knowledge flow. With that said, a focus on retention of tacit knowledge of the respective organizations, systems, and products should be a central consideration in M&A activities.

Although products and systems are described in many documents (explicit knowledge), there is a tremendous amount of knowledge that is only located within the people of the organization, who are keepers of the know-how and the "know-why" behind decisions and ways of working. The ISPE KM GPG identifies the importance and impact of tacit knowledge and the fact that it is often underappreciated [1]. Research by McKinsey demonstrates that in technical fields, tacit knowledge could comprise upwards of 70% of the knowledge [11]. Junker and colleagues discuss the prevalence of tacit knowledge in healthcare, noting similar numbers may be found in the biopharmaceutical sector [12].

ROCK is a methodology to capture the know-what, know-who, and know-why (tacit knowledge) for those changing roles or leaving the organization. The development of ROCK as a KM tool by Royal Dutch Shell Corporation was discussed in a KM best practice report as a KM process to capture tacit knowledge [13]. The concept of ROCK has been leveraged by multiple companies, including pharmaceutical companies such as Merck & Co., Inc. Merck noted that after the 2009 integration of Schering-Plough, it was recognized that "even tenured experts knew only a fraction of the expertise available in the new, expanded global organization" [14].

CONCLUSION

KM has been identified in pharmaceutical regulatory guidance as an enabler to a PQS. In addition, KM has been identified as an enabler to organizational effectiveness and efficiencies. Considering the continuing prospects for M&A in the pharmaceutical industry, it has never been more important for effective

Table 2: KM tools and approaches for M&A E2E knowledge transfer.

KM Tool/Approach	Acquisition Agreement/announcement through Day 1, including plans for integration of people, process, technology, etc.	Integration/Value Capture Execute on plans and achieve synergies; may include movement of people, products, sites, etc.
Knowledge Mapping	Understand what knowledge exists in functions and the flow of knowledge through business processes	Opportunities to optimize knowledge flow through new or modified business/technical processes (process knowledge mapping)
Taxonomy and Search	Extend taxonomy to cover scope of the acquisition (e.g., new products, devices, etc.)	Apply taxonomy and search to rapidly integrate and make visible knowledge repositories across new integrated entity
Expertise Location	Understand who key experts are relative to products/topics being transferred to ensure holistic knowledge transfer	Understand who key experts are relative to products/topics being transferred to ensure business continuity
After Action Review/ Lessons Learned (AAR/LL)	Perform AAR/LL on inline activities for M&A to identify efficiencies and de-risk	Continue to identify, share, and seek lessons to improve processes
Community of Practice (CoP)	Serve as entry point for team members transferring for specific knowledge that reside in CoP topics	CoPs help expand the network for new colleagues, any new technology acquired can be rapidly shared, discussed, and leveraged
Knowledge Transfer (KT) Plan	Plan to outline the objectives, timelines, tools, and processes to be utilized to capture knowledge to be shared and transferred	
Retention of Critical Knowledge (ROCK)	Assess risk areas (topics and people), develop ROCK plan; use for retention targeting	Execute ROCK as needed based on risk tolerance

KM to be employed. To assist in deploying KM, Table 2 summarizes opportunities to leverage KM tools and approaches to enable M&A E2E knowledge transfer.

In a 2018 publication, both Pfizer and Merck & Co. shared case studies of KM implementation using many of the KM tools and approaches in Table 2 [15, 16]. Because many of these tools and process are commonly known and well-documented in the literature, the author suggests these tools and approaches could be leveraged into other areas of the pharmaceutical business, presenting future opportunities for KM in M&A and knowledge transfer.

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About the author

Paige E. Kane, PhD, CPIP, is a member of the Technical University Dublin Pharmaceutical Research Team. She is an industry leader with over 29 years of experience including Merck & Co., Genetics Institute, Wyeth, Pfizer, Monsanto, and US government, spending many years leading knowledge management programs and approaches for the pharmaceutical industry. Paige previously led quality systems groups focusing on automation compliance, data integrity, computer validation, and change control during startup and operations for biologics facilities in the US and Ireland. She has been a member of multiple industry guidance author teams and global industry Communities of Practice (GAMP® and Biotechnology) as well as leading other strategic teams for industry, including the ISPE *Good Practice Guide: Knowledge Management in the Pharmaceutical Industry* team. She is a co-editor/contributor for "A Lifecycle Approach to Knowledge Excellence in the Biopharmaceutical Industry" (2017) and holds a PhD in pharmaceutical and regulatory science from Technical University Dublin. Paige has been an ISPE member since 2000.

KNOWLEDGE CENTERS IMPROVE

Knowledge Capture and Sharing

By Noah Davison

As the industry experiences significant changes to the way we do business, knowledge capture and sharing are more important now than ever before. The maturing digitalization of the biopharma industry's business and processes is creating an increasingly data- and information-rich environment that requires more effective mechanisms for sharing data and information. The Knowledge Management team at Amgen created knowledge centers to make it easier to get the right information to the right people at the right time.

In these uniquely busy and challenging times, it is easy for knowledge capture and sharing to fall in the list of priorities. This presents a tremendous opportunity to develop the means to embrace and enable the creation, democratization, and reuse of institutional knowledge, and to facilitate its continuous growth. Communication via a variety of channels has emerged and evolved as a critical skill for not only the day-to-day, "keep the lights on" activities, but also for knowledge sharing and consumption.

To that end, the Knowledge Management team at Amgen has innovated knowledge capture and sharing in multiple ways. One highlight that illustrates this innovative processing is the creation of knowledge centers as a primary use case within our Knowledge MarketPlace. The Knowledge MarketPlace is an operations-wide SharePoint knowledge repository and search tool. Knowledge centers are topic-based pages within the Knowledge MarketPlace. We define knowledge centers as a one-stop shop for topic-based information that is relevant to particular functions, is continuously curated, includes established taxonomy for categorization and findability, and employs content collections. All timely and relevant knowledge is surfaced in the knowledge centers for even greater ease of access.

When we decided to create the knowledge centers, we knew we needed a good partner for a proof of concept project. Fortunately, with the Technology Transfer Global Network (TTGN), we found a collaborator that was interested and ready to improve its ability to capture and disseminate lessons learned. Technology transfer consists of all activities required to transfer a defined manufacturing process into a manufacturing facility, beginning with site selection and concluding with regulatory licensure. TTGN is a collaboration system of experts who meet regularly to discuss lessons learned and share knowledge pertaining to all activities within the technology transfer life cycle.

PROJECT SUMMARY

TTGN collaborated with our team to build a scalable and sustainable system that would satisfy the TTGN requirements and deliver desired business value. This case study describes the problem, opportunity, process used, and created outcomes and business benefits.

PROBLEM

TTGN had disparate locations for the capture and storage of lessons learned, and much of the information was also tacit knowledge only. Varied processes and tools were used to capture and share information. The Knowledge MarketPlace wasn't used as effectively as possible; therefore, the content captured was not standardized or shared effectively. Additionally, the timing varied for the lessons learned captured and the facilitation timing of lessons learned tended to occur retrospective to the technology transfers. Culturally, this wasn't always part of the process, and as such, teams were not using a consistent approach to capture and share lessons learned.

OPPORTUNITY

In an effort to drive continuous improvement of our processes and practices, the team recognized the need to develop competency in the area of knowledge management. This included aligning on a knowledge management strategy and making the necessary tools and resources available. After benchmarking and analysis, the team decided to build a lessons learned knowledge capture system by leveraging an out-of-the-box SharePoint platform.

With this functionality, lessons learned became available to anyone, at any time, in any function or workstream, making lessons learned capture and sharing easy. Building the system brought the Knowledge Management and Technology Transfer teams together—two groups motivated to collaborate and create a knowledge management module that is easy to use, has a pleasing and effective user interface, and meets the customers' needs and requirements.

PROCESS

An Agile/Scrum approach was employed to create a development plan and manage project execution. Using an Agile/Scrum framework ensured an outcome that would be aligned with stakeholder needs, flexible, and easy to change in stride as new opportunities arose.

The Knowledge Management team performed a voice of customer (VOC) study that helped identify all user and system requirements (wishes and desires) and facilitated workshops with the TTGN workstream leads and subject matter experts. From the VOC, we learned what the ultimate users preferred as a desired end state, including a lessons learned contribution form that would be easy to use, with autofill fields, intuitive dropdowns, predictive text programing, workflow communications to appropriate users, and the ability to save previous info in the form when making additional entries for the same transfer or project.

The quality of the knowledge captured has improved tremendously. The use of the new system has made knowledge capture more routine and implicit. The capture and dissemination of tacit knowledge, as it pertains to technology transfer, is becoming an issue of the past.

From a lesson learned capture perspective, the team wanted a solution that captured all pertinent information and quantified benefits of the lesson learned, was easily filterable and keyword searchable, that functioned as a collaboration tool that collected commentary and shared data with the right people within the system itself, and could be used as a presentation tool in place of PowerPoint presentations.

The teams conducted knowledge mapping exercises to identify and map the critical business processes with the relevant knowledge elements to create alignment and identify gaps in the availability and quality of data and information. The team further refined the gap analysis using a people, process, technology, and content (PPTC) framework, highlighting the relationship to the current state, gaps identified, and proposed design factors, which were later translated to specific design requirements and a knowledge management solution framework for each capability.

FEATURES

- A topic-based, "one-stop shop" knowledge center specific to technology transfer that answered all the questions raised during the requirement gathering stage.
- Searchable, filterable, viewable, editable, and presentable lessons learned with consistent ontologies.
- Workflow notification sent to workstream leads whenever a "high" impact ranked lesson learned is added in case it's an issue that needs to be reviewed immediately.
- Extracurricular features on knowledge centers such as "contribute," "search," pertinent knowledge assets, analytics/metrics reports, collaboration tools, pertinent instructional videos from users, links to other pertinent sites, interdependent processes, external industry lessons learned, and links to subject matter experts.

OUTCOMES/BENEFITS

- The necessary knowledge is captured and made available in the form of lessons learned.
- The quality of the knowledge captured has improved tremendously. The use of the new system has made knowledge capture more routine and implicit. The capture and dissemination of tacit knowledge, as it pertains to technology transfer, is becoming an issue of the past.
- The team has also realized that the knowledge center is not only a knowledge-sharing tool but also a key mechanism to drive continuous improvement of our processes and practices.
- TTGN is actively capturing lessons learned at multiple stages throughout the technology transfer life cycle, thus facilitating greater knowledge flow everywhere it's identified, created, captured, shared, and reused.
- In just a few months, almost 500 lessons learned were added to the new centralized database. Of those, 35 have been given a "high" impact ranking. The quantified benefits, thus far, for only three of those "high" ranked lessons learned captured directly equate to a cost avoidance of $5.5 million in waste reduction attributed to labor hour savings, specifically in the form of delay prevention, cycle time reduction, "right the first time" processing, and mistake proofing implementation.
- Rather than creating multiple PowerPoint slides from memory of issues and lessons learned that happened months ago, teams are using the system in real time in their team meetings, and if necessary, immediately for "high" impact ranking. They simply submit the issue in the system, perform a review, and make edits if necessary. Comments are captured with workflow notification to necessary recipients.

CONCLUSION

As TTGN has realized the benefits of knowledge centers, so too have many other groups and workstreams at Amgen. Because of the positive response and frequent use of the Lessons Learned Knowledge Center, the Knowledge Management team has had an influx of requests for additional knowledge centers. At the end of 2021, we had a total of 44 topic-based knowledge centers with topics ranging from operational readiness to operational excellence and everything in between. To this end, new knowledge centers have been added, including those that specifically capture lessons learned from many functions other than TTGN. The Lessons Learned Knowledge Center is a simple concept that makes knowledge capture and dissemination easy and fun.

About the author

Noah Davison is a Business Performance Manager and Product Owner of the Knowledge MarketPlace in the Operations Data Sciences and Knowledge Management group at Amgen. Previous to this role, Noah worked in a Corporate Operational Excellence consultant role supporting all operations functions through the journey of lean transformation. Prior to Amgen, he was founder and owner of the Mogollon Brewing Company in Flagstaff, Arizona. He received his bachelor's degree in architecture from Colorado State University.

WEBINAR: Knowledge Management Insights and More

By Stephanie A. Friedrichsen

On 26 January 2022, representatives of the author team for the ISPE *Good Practice Guide: Knowledge Management in the Pharmaceutical Industry* held a webinar to provide an overview of the guide, which published in May 2021. Over 300 attendees joined the authors as they discussed key concepts of knowledge management (KM), linkages to current regulatory guidance, KM methods and tools, and relationships with complementary disciplines. Throughout the webinar, the authors polled the audience on topics around participants' current understanding of KM, the current state of KM initiatives in the participants' organizations, and what other processes the audience felt could benefit from additional KM focus and application.

In 2018, the ISPE KM Good Practice Guide (GPG) team started their partnership with the Product Quality Lifecycle Implementation (PQLI®) Steering Committee. In 2019, they received approval from ISPE to officially form a team and began authoring the content in 2020. After addressing industry comments, the guide was published in May 2021, and the author team plans to continue to partner with ISPE through webinars, blogs, and potential future opportunities for training.

One of the main drivers for the KM good practice guide (GPG) team was to establish a foundational understanding of KM and how KM concepts apply specifically to the pharmaceutical industry. Although KM was first discussed in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q10 in 2008 and again in ICH Q12 in 2020, only 11% of the webinar's audience members stated that KM efforts were well in progress within their organizations, and 41% were still investigating KM but hadn't started yet. The webinar polling results demonstrate the value and need for fundamental and practical knowledge in this space.

KM AND THE PHARMACEUTICAL INDUSTRY

Although KM and quality risk management (QRM) are both identified as enablers of an effective product quality system (PQS), the definitions of KM and KM for pharmaceutical manufacturing have remained unclear. Polling during the webinar showed that only 33% of the audience felt confident they had a good understanding of what KM is, with 28% acknowledging they did not have a good understanding, and with the remaining 39% unsure of their level of understanding. The webinar expanded on the definition of KM per ICH Q10 by providing an additional definition commonly used by KM practitioners across industries that embraces the needs of the knowledge user as well as managing knowledge for the business benefit:

> The application of a structured process to help information and knowledge flow to the right people at the right time so they can act more efficiently and effectively to find, understand, share, and use knowledge to create value [1].

The team also expanded on the term "knowledge" with two concepts:

- Types of knowledge: Explicit, which includes knowledge that is written down, and tacit, which is the knowledge that remains in our heads. Tacit knowledge accounts for the majority of our overall knowledge, but can be difficult to transfer (e.g., decision rationales), and benefits greatly from KM methods and tools to identify and retain.
- Data, information, knowledge, and wisdom (DIKW) diagram, in which the team discussed the distinctions between these descriptions and noted it is important to understand that data and knowledge are not synonyms.

The webinar provided additional insights into the content of the GPG, highlighting the guide's deeper dives into topics, including KM and the pharmaceutical quality system; a framework for linking KM to risk management; a KM process model; the pharmaceutical product knowledge life cycle; and general Principles & Common Approaches for Digital KM.

More than two-thirds of the guide's content contains appendices with practical details on how to get started with KM; measuring maturity, methods, and tools; common templates; and pharmaceutical-specific case studies to expand the industry's foundational understanding and application of KM.

METHODS AND TOOLS

The webinar expanded into more details on KM Methods & Tools discussed in the guide, which include description, value, use, and case studies for further study of Communities of Practice (CoPs); storage and search; lessons learned; knowledge mapping; and expertise location.

The authors also discussed the value of thinking of KM as another discipline within an organization's capabilities. Complementary disciplines include QRM, organizational change management, operational excellence, content and information management, and learning and development. The webinar further explored the capabilities of operational excellence and knowledge management.

KM is an enabler for two aspects of the pharmaceutical industry: First, as an enabler to the PQS, and second as an enabler to operational excellence (OpEx). KM and OpEx share synergistic goals and concepts, as both disciplines:

- Achieve efficiency and optimization
- Enable organizational objectives
- Share a focus on flow
- Look to enable and engage the workforce
- Utilize standard approaches and tools built into daily processes

Where OpEx looks to optimize product and process flow, KM seeks to optimize organizational knowledge flow. OpEx may leverage Lean and Six Sigma concepts to reduce waste and variation to support sustainable, efficient processes; KM leverages methods and tools to sustain knowledge and enable business continuity.

The authors highlighted that the guide explores this concept further in two aspects: The use of methods and tools to address waste and inefficiency in the flow of knowledge (e.g., search and surface of information, or faster, informed decisions); and business continuity in knowledge transitions (e.g., new molecular entities, mergers and acquisitions, commercialization, retirements, and transitions).

The audience was asked to identify their top three processes that could benefit from additional KM focus and/or application. These were the leading processes identified: continuous improvement, change management and post-approval changes, and technology transfer.

QUESTIONS AND ANSWERS

Audience engagement throughout the webinar was high, and multiple questions were submitted with the following themes:

- Measures for KM
- Navigating organizational change management

Table 1: Responses to webinar questions.

Question Theme	Insights from the KM GPG
Are there common measures for KM?	Like many initiatives, the measures for KM are dependent on how an organization wants to deploy or leverage KM. For example, diagnostic measures may help articulate the current state of a KM program (using a KM maturity model), or using a knowledge map to measure criticality and flow of knowledge in a process to identify and act on areas of poor knowledge flow. Overall health of other KM methods and tools could focus on signals that show adoption and overall "health," such as a measure of engagement for a Community of Practice. There is no single "best" measurement to cover all KM initiatives: Evaluate first how KM will be used in the organization, as it is ultimately an enabler. Then identify the measurements that will work best.
What are the key organizational change management considerations for KM?	The guide contains an appendix dedicated to developing an effective KM initiative, including considerations for organizational change management (OCM). The guide discusses five key OCM recommendations: • A planned structure that provides sponsorship • Governance • Clearly defined roles • Linkage of the KM initiatives to organization and team objectives • OCM focused on supporting colleague engagement
Can you expand on the relationship between KM and training?	Training, or learning and development, is a complementary discipline to KM. Training utilizes content designed with adult learning theory to support employee skill development and qualification. This is a form of structured, formal knowledge transfer recognized by the KM discipline. However, by this design, training has a primary focus on the transfer of an organization's explicit knowledge and remains focused on training content as a primary knowledge asset. While KM recognizes that training is one of many ways to transfer knowledge, there is a focus on overall knowledge flow as an enabler to the organization's ability to achieve objectives. The unique differentiator between KM and many disciplines is the ability to identify, extract, and leverage the tacit knowledge of an organization. In this manner, the training team may be a recipient of a KM initiative's outputs, and the knowledge assets extend into the overall knowledge of an organization. ISO 30401 Knowledge Management Systems [2] further expands on the differences between KM and many other disciplines.
What are the common roles and responsibilities for KM?	The guide's appendices outline common roles, descriptions, and responsibilities. What roles an organization utilizes may also be based on how the organization will utilize and deploy KM. Common examples include (but are not limited to): • A KM sponsor, who is a leader within the organization that champions the KM initiative • KM team members that develop and deploy KM methods and tools • Knowledge stewards who are responsible for a repository of knowledge • Knowledge workers in the business unit utilizing KM that use their expertise, education, and experience to solve work problems and manage knowledge as an asset
What role does technology/software play in KM in today's digital era?	Digitization is a prominent topic across the pharmaceutical industry; the guide has a chapter dedicated to the discussion of digitally enabled KM. A technology solution does not guarantee a successful KM initiative, and an organization can begin a KM initiative independent of a software solution. Technology should be viewed as an enhancement to a KM program, and the guide recognizes that digital solutions may make data, information, and knowledge easier to manage and find faster. If designed with KM in mind, these technologies can impact the speed at which an organization can make informed decisions. The guide further explores common digital approaches, technologies, and characteristics for digitally enabled KM.

- The relationship between KM and training
- Roles and responsibilities
- Technology

Table 1 provides responses to the questions that the authors could not cover during the webinar.

For More Information

For more information about the ISPE *Good Practice Guide: Knowledge Management in the Pharmaceutical Industry,* visit https://ispe.org/publications/guidance-documents/good-practice-guide-knowledge-management-pharmaceutical-industry

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About the author

Stephanie A. Friedrichsen joined Eli Lilly & Company in 2008 as part of PR&D's Clinical Trial QA group, where she was the process owner for collaboration partner qualification, oversight, and activities such as person in plant. In 2015, she joined the Global Serialization Program, where she owned the strategic plan for knowledge management, training strategy, and lean Six Sigma projects. Steph recently joined Lilly's Indianapolis Parenteral Manufacturing team in March 2022 as a Competitive Continuous Improvement Coach. Both an industry author and speaker on KM, she was a core team member on the ISPE *Good Practice Guide: Knowledge Management in the Pharmaceutical Industry* and has spoken at events such as APQC's KM Conference on Lilly's use of KM to deliver serialization and IFPAC on behalf of the BPOG KM workstream. She currently co-chairs the IFPAC KM session and continues to engage in ISPE through the KM GPG team. Steph has been an ISPE member since 2019.

COMMUNITIES OF PRACTICE PROFILES: Meet the PAT-LCS CoP

By Marcy Sanford

ISPE has more than 17 global Communities of Practice (CoPs) where members can connect with each other. Professional CoPs for Emerging Leaders and Women in Pharma® provide the opportunity for members to network with colleagues from around the globe. Technical CoPs offer networking opportunities and provide a connection to collaborate with international peers on topic-specific content. *Pharmaceutical Engineering*® is initiating an ongoing series of CoP profiles, starting in this issue with the Process Analytical Technology & Lifecycle Control Strategy (PAT-LCS) CoP.

The PAT-LCS CoP has more than 3,000 members and is led by a diverse steering committee, with representation from Central Europe, Turkey, Singapore, and North America. The group focuses on developing content to benefit members of ISPE in relation to the use and standardization of PAT, and the field of lifecycle control strategies. Members from the Steering Committee can often be found at ISPE's Annual Meetings in Europe (see Figure 1) and the US presenting on their latest initiatives and outcomes.

The CoP contributes to conferences, often with separate sessions, and most recently has hosted the webinar "Unravelling Manufacturing Control Strategies: Maturity Model and Case Studies." Members from the steering committee are also leading the team writing *ISPE Advancing Pharmaceutical Quality (APQ) Guide: Process Performance and Product Quality Monitoring Systems*, which, as the most recent output of the CoP, will include a control strategy maturity model it developed. Line Lundsberg-Nielsen, PhD, Managing Consultant, NNE, and Chair of the PAT-LCS CoP talked with *Pharmaceutical Engineering*® recently about the CoP.

Figure 1: Line Lundsberg-Nielsen, CoP Chair, and Steering Committee members Christian Wölbeling (center) and Eric Urau (right) at the 2022 ISPE Europe Conference.

She said anyone who is interested in learning more about PAT-LCS concepts can benefit from joining the CoP. Lundsberg-Nielsen sat down with PE to answer a few questions about the CoP.

WHAT ARE THE CoP'S AREAS OF FOCUS?

As our name suggests, we focus primarily on PAT and the life cycle of control strategies in commercial manufacturing. We're looking at advanced control strategies based on real-time PAT applications, modeling, and simulation tools and consider the evolution and application of the control strategy throughout the product life cycle as more product knowledge and process understanding are captured.

When the CoP was launched in 2005, it was purely focused on understanding the role of PAT and its applications for gaining

Figure 2: Opening slide from the "Unravelling Manufacturing Control Strategies: Maturity Model and Case Studies" webinar.

process understanding versus applications for process control purposes. Following the trends of that time, the focus was particularly on small molecules; for example, active ingredient synthesis and tablet manufacturing.

The pharmaceutical industry since then has adopted many of the PAT concepts into daily routine and today it is very difficult to run a continuous manufacturing process without PAT as a tool for live monitoring of product quality and process performance. Different PAT analyzers installed in the process equipment combined with mathematical models are therefore being used extensively to control the output of a process step, typically monitoring critical quality attributes (CQAs) of the intermediate and/or finished product, providing a more efficient and faster quality control in contrast to analyzing samples in the laboratory. Many of the technologies we use are based on spectroscopy, such as NIR, MIR, and Raman, just to mention a few of the more popular ones.

Obviously, the knowledge and experience gained with small molecules has been translated to large molecule processes—so has the interest of the CoP. Currently this is one of the key drivers in the PAT portion of the CoP, as large molecule processes are of higher complexity.

The LCS portion of the CoP was a logical extension of the existing working topics; as with the capabilities of PAT, additional focus was needed on the control strategy as a whole and how it can be maintained and improved throughout the product life cycle to accommodate for variations in, e.g., raw materials and wear and tear of process equipment and not only on the PAT technology. The scope and name of the CoP was therefore changed from PAT to PAT-LCS. This was also an attempt to support the—at that time newly born—ISPE Pharma 4.0™ initiative, where the control strategy plays a major role.

The control strategy is important because it's the recipe that tells you how to make your product, how to produce it, how to control it, and how to get the right product quality.

WHY IS THE CoP'S WORK IMPORTANT TO THE PHARMACEUTICAL INDUSTRY?

The control strategy is important because it's the recipe that tells you how to make your product, how to produce it, how to control it, and how to get the right product quality. What we want to do is to have an inline and real-time-based automated control strategy by applying data analytics and modeling tools to both PAT data and process data, so the process can be adjusted and optimized in real time, ensuring that patients always get the same high-quality

medicinal product within the shortest time. We believe that by focusing on real-time control and improvement, the industry will be able to achieve this goal.

This is the direction that more companies are taking now. It has taken us many years to get where we are today, and there is still a lot to do to encourage and support those companies that have not started yet. Finally, we also need to make sure that the evolution is mutually recognized between the industry and regulators.

TELL US ABOUT THE WEBINAR THE CoP PRESENTED IN MARCH 2022

We were originally scheduled to present this research at the 2021 ISPE Annual Meeting & Expo, but most of the presenters live in Europe and were not able to travel to the conference. To share our work with the community, we decided to convert this into a webinar instead (see Figure 2), "Unravelling Manufacturing Control Strategies: Maturity Model and Case Studies."

Control strategies are becoming more important, and companies must have many different strategies in place to secure robust manufacturing, including monitoring and review of manufacturing data to ensure product quality throughout the product's life cycle. Our CoP examined the different impact areas and strategy implementation, how they are related, and determined the benefits of different strategies in terms of speed, efficiency, and agility. We then asked the question, "What are the capabilities required for applying these control strategies?"

In the webinar, we presented a life-cycle control strategy maturity model that can identify opportunities to improve new and existing product control strategies. The model links digital maturity and control strategy maturity to enable process robustness and product quality assurance in an efficient manner. The model includes different capabilities such as development approaches, digitalization, analytics including PAT, modeling, data analytics, control regimes, and release strategies.

Control strategy maturity has been discussed by different industries and organizations but never formulated in detail in the pharmaceutical industry. With this model, we have tried to bridge the different control strategy approaches and, in particular, link the FDA control pyramid, Pharma 4.0™ digital maturity, and the use of PAT and real-time release testing (RTRT).

WHAT DO YOU ENJOY ABOUT BEING A VOLUNTEER WITH ISPE?

ISPE has been very important in developing me professionally. I have learned a lot from my ISPE connections, particularly when I've been able to work with colleagues from other pharmaceutical companies. When you can collaborate and discuss with others, you learn from them. Sharing knowledge is important because you cannot learn everything you need to be successful by yourself or just by reading articles or taking courses. When you are trying to solve a problem, it really helps to hear what others have done.

For example, through ISPE I met one of the PAT pioneers within a globally operating pharmaceutical company. At that time, I was working at a smaller pharmaceutical company, and I invited him to come and talk to our production and development senior management about what his company had achieved by applying PAT. This talk was an eye-opener and my senior management gave me the go-ahead to kick off a PAT program. I became responsible for implementing PAT and quality by design (QbD).

This connection through ISPE was an amplifier for my professional career. It is all about having a good network to work and share knowledge with, and I get that through ISPE.

One of the things I try to do is to support our emerging leaders in our CoP so they can get exposure by talking at conferences, writing, and presenting to expose them to members working in similar endeavors. I try to connect them with other people.

WHAT DO YOU SEE AS THE FUTURE OF THE CoP?

Right now, the CoP has strong momentum. One of the CoP Steering Committee members suggested we discuss PAT modeling and data analytics using Open Source software and new digitization efforts. We are hoping to kick off some town-hall-type meetings for the CoP members at large. We would love to see more robust conversations on our forum in ISPE Engage. We really encourage members to get involved, to ask their questions, and to propose content that they want us to focus on.

For more information

To join the conversation about Process Analytical Technology and Lifecycle Control Strategy, visit ISPE Engage at ISPE.org/membership/communities-practice

About the author

Marcy Sanford is Publications Coordinator for ISPE.

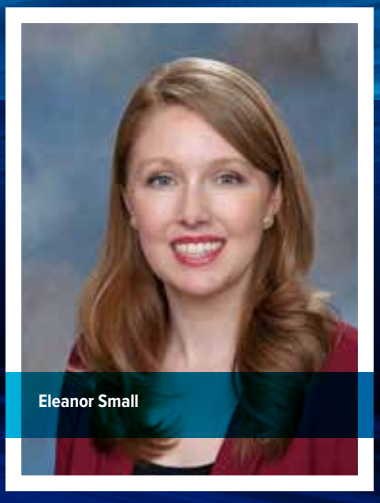
PE Magazine Wants Your P+E!

Tell us about your Chapter and Affiliate events and conferences, trainings and Women in Pharma® meetings, Emerging Leaders activities, and Communities of Practice and Special Interest Group work, and we'll share it with all of ISPE in *Pharmaceutical Engineering*'s People+Events (P+E) section. Please submit articles and short items for ISPE Briefs to ssandler@ispe.org—ISPE Briefs can be up to 400 words, articles can be up to 1,000 words. Photos are welcome: at least 300 dpi or >1 MB.

ISPE 2021 MEMBER OF THE YEAR

Leading With Creative Thinking and Adaptability

By Marcy Sanford



Eleanor Small

Eleanor Small, the 2021 recipient of the ISPE Max Seales Yonker Member of the Year award, uses her creativity and adaptability to discover new solutions in her work and to help ISPE succeed. She received the honor at the 2021 ISPE Annual Meeting & Expo in Boston, Massachusetts.

The award was introduced during the Member Breakfast session at the conference by Joanne Barrick, 2020–2021 ISPE International Board Chair. Barrick commended Eleanor's leadership and outstanding commitment to ISPE, saying it proved vital to the continued success of the ISPE Delaware Valley Chapter (DVC). She noted that during the pandemic, Eleanor capably led transfer of responsibilities of the Chapter's financial controller to a new two-person model, utilizing the treasurer and director of finance. She instituted improved documenting procedures and committee chair responsibilities leading to better controlling of expenses. This inspired the Chapter with strength, stability, flexibility, and resiliency, Barrick said.

Having already built the virtual infrastructure required for chapter webinars before the pandemic, Eleanor was able to move the Chapter into fully virtual programming quickly and effectively, helping fill the financial void created by cancellation of the Annual Symposium and Exhibition Show. She also started initiatives to support smaller, decentralized Chapters by sharing educational programming and by simulcasting local webinars. Her actions successfully stabilized the Chapter while enabling excellent virtual content for its members. She accepted a nomination for a second consecutive term as Chapter President, providing further stability to the Chapter. Barrick noted that even through the pandemic, the DVC maintained the highest membership retention rate for any US Chapter.

BORN INTO A HEALTH CARE FAMILY

With a father who was a doctor and a mother who is a nurse midwife, Eleanor knew she wanted to do something in the health care field, but it took some exploring to determine exactly what. "Health care is in my family. In school, I liked math and physics better than biology, so I was trying to find a place best suited to my strengths in the health care industry. In college, I looked at biophysics and chemical engineering."

Eleanor earned her PhD in chemical and biochemical engineering from Drexel University and her BSE in chemical and biomolecular engineering from Johns Hopkins University. As a research fellow at Drexel, her research focused on ultrasound-triggered drug release. Her fellowship also allowed her to co-develop hands-on enhanced curricula with the School District of Philadelphia science teachers for high school science and engineering classes.

"I've had some amazing teachers in my life who were so supportive when I was in high school; teachers who really encouraged me to continue in science," Eleanor said. "I also had parents who were very encouraging, and I know not everyone gets that kind of support, so it is vital to me that everyone has at least one person who says, 'Yes, you can. You can take this further.' We know junior high and high school are pivotal moments when teens decide if they are going to continue in science.

"Learning science out of a textbook is not the most effective way for me to learn. Science is meant to be hands-on and experimental. As part of my fellowship at Drexel University, I got to go into the classroom with teachers, work side-by-side with them to create stronger hands-on science classes, and bring science to life. It was a great experience."

STEM INDUSTRY CAREER

After graduate school, Eleanor joined Johnson & Johnson Consumer Health, which has given her the opportunity to continue her

"The part I love the most is knowing that the science that I work on is serving a purpose. That's why we are in these roles. I love science, but I have always believed in science that serves."

commitment to helping students stay with STEM. "The company encourages employees to get involved; it is part of our credo. I work with an employee group that focuses on STEM education for underrepresented students, especially girls, in underserved communities. I think we lose some amazing minds every day because they are not encouraged."

As a Research and Development Manager, Product Development, with Johnson & Johnson Consumer Health Self-Care, Eleanor focuses on meeting consumer needs for over-the-counter pain relief and has extensive experience in consumer insight-driven, end-to-end product and process development meeting cGMP requirements. "The part I love the most is knowing that the science that I work on is serving a purpose. That's why we are in these roles. I love science, but I have always believed in science that serves.

"For me, having a clear view of the purpose of the science you are working on is important. In consumer health care, we are even closer to our end user than you might be in other areas, because a lot of the research I do is focused on DIY or preventive health care. This kind of innovation demands a fast turnaround, and often poses the challenge of creating a product with a desirable user experience while also ensuring efficacy."

Eleanor has launched more than 12 new products under Johnson & Johnson Consumer Health's iconic brands. She leads global cross-functional teams responsible for product design/development, scale-up, launch, and life-cycle management of new and current products, and has experience working with monograph drugs, class I and class II medical devices (engineered and formulated), cosmetics, and combination products. "With new products, it is really fun to try to think creatively—that is part of the art that goes into science. I'm trying to take a known treatment and deliver it in an experience that is better, so I have to think about not just the science but also the consumer's experience."

Eleanor has developed new medical device class II wound care products for the Japanese market, and new formulas for monograph drugs, including a milder version of J&J's leading mouthwash. The base of this formula continues to be used to develop new flavors for the product line, providing a variety of appealing options to help new users build healthy habits. Her most recent accomplishment is the newly launch Digital Ear Scope from J&J's leading pediatric pain care brand. The digital otoscope works with a smartphone and companion mobile app to help parents and their children manage ear health by connecting them with healthcare professionals. The product is the first medical device plus app for J&J consumers.

ISPE CONNECTIONS

"Since I am on the R&D/development side, the aspect of ISPE I enjoy the most is that it connects me with different sides of the business: regulatory, quality, and manufacturing. It has been a huge opportunity to see the world through another perspective, and to learn how quality or validation groups work. It has changed how I work; I ask questions like 'is this scalable?' and 'what do I need to think about and write down now so the next person doesn't have to guess?' Creativity is important, but if you don't have regulatory approval, the product is never going out the door." Eleanor enjoys learning about what is important to colleagues and feels it is important to do so. "It may not be your immediate responsibility, but you should think about it."

Thanks to her adaptability and creative thinking, the DVC stayed successful during the pandemic. "We had already been experimenting with digital concepts for educational sessions in the Chapter. It put us in a powerful position when COVID-19 hit because members trusted we knew what we were doing since we had experience." She noted that digitalization became part of running the business of the Chapter, not just its programs. "We started creating a digital archive and some of that was driven by the overall digital mindset we were trying to get into. We started thinking of ways we could do better. It is very important to always be adaptable and to want to change for the better, not just change because we have to.

"In consumer health, you have to want to change to meet consumers' needs. At ISPE, we have to want to change to meet members' needs and think about what they want and what they expect. This has been a really important year, a really important time to be focused on members and changing for the future."

ABOUT THE AWARD

Eleanor exemplifies the spirit of the Max Seales Yonker award, noted Barrick in her remarks at the 2021 ISPE Annual Meeting. The award honors ISPE members who have dedicated themselves to excellence and service to the industry and ISPE. It was named in memory of ISPE member and industry leader Max Seales Yonker, who died in 2005. Barrick said during the award presentation, "The memory of Maxine Yonker reminds us that we are all patients, and it reminds me of the vital work that each one of you do to advance the development, production, and delivery of a safe and reliable drug supply."

About the author

Marcy Sanford is Publications Coordinator for ISPE.

New APQ Guide: Develop a Robust and Efficient Change Management System

Effective and timely management of change throughout the product life cycle enables quality improvement and is critical to patient safety, supply reliability, and operational effectiveness and efficiency. The *ISPE Advancing Pharmaceutical Quality (APQ) Guide: Change Management System* provides a quality management framework for assessing and advancing change management (CM) system maturity level by evaluating areas such as CM documentation, CM metrics, governance, management oversight, and more.

"Pharmaceutical companies are required to have a change management system in place, but an inadequate one may result in ineffective changes that require rework or missed opportunities," said Guide Lead Lori Chelemedos, Founder/Principal Consultant, Pac-Side LLC. "This guide focuses on how to evaluate and optimize the system a company has, provides tools that can be used to improve the system, and offers guidance on how to improve and develop a change management system that is appropriate to a company's maturity level."

This is the third guide in the APQ Guide Series, which is part of ISPE's Advancing Pharmaceutical Quality initiative. The APQ Guide Series is aligned with international initiatives that promote quality excellence, as well as the FDA's interest in quality management maturity. Other guides in the series explore corrective action and preventive action (CAPA), management responsibilities and management review, and process performance and product quality monitoring systems.

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

—Marcy Sanford, Publications Coordinator

Meet the ISPE STAFF

ANNA RILEY

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

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

I lead our Member Services team, who you have likely interacted with over the phone, via email, and at conferences. We work together to make every interaction with ISPE a great interaction. I also manage ISPE Engage to keep it a strong peer collaboration benefit for our members.

What do you love about your job?

My job offers me the opportunity to collaborate and create with almost every ISPE staff member in an effort to better serve our members. I absolutely love building relationships and getting creative with not only the ISPE team, but also with our membership. I am fascinated by the work you all do to shape the future of pharma!

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

I love spending free time with my husband and our seven-year-old daughter. We like to hunt down live music events, get together with friends, and explore our beautiful city of Tampa, Florida. As a trained yoga teacher, I also spend a good amount of time practicing yoga either at home or in group class settings. Namaste!

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AI GOVERNANCE AND QA FRAMEWORK:

AI Governance Process Design

By Elias Altrabsheh, Martin Heitmann, FRM, and Albert Lochbronner

Artificial intelligence (AI) has the potential to benefit the pharmaceutical industry and its GxP-regulated areas. Several pharmaceutical companies are currently running digital pilots; 90% of large pharmaceutical companies have initiated AI projects [1]. However, their implementation remains limited, mostly due to a lack of robust validation procedures. Hence, there is a need to develop a robust governance framework to ensure that integration of AI into workflows is possible while simultaneously ensuring that evaluation standards are still met. The proposed framework presented in this article provides a general organizational and procedural structure for developing and sustaining AI solutions in GxP-relevant contexts.

The framework's holistic concepts can be integrated with current regulatory developments that are driven by both international and national regulatory bodies [2–6].

After having published the AI maturity model [7] with regard to autonomy and control, including a dynamic development path along the life cycle of an AI application, we continue our article series with our AI governance and quality assurance framework. This framework provides a general organizational and procedural structure for developing and sustaining AI solutions in GxP-relevant contexts.

Our holistic concept covers the focus areas shown in Figure 1, packaged in an AI quality assurance master plan. This overarching structure enables harmonization across AI initiatives from a top-down approach while retaining the flexibility to tailor the operational procedures for each initiative that would be governed by this master plan and facilitates respective cooperation across AI initiatives:

- Corporate culture: The development of AI solutions generally requires a shift in mindset by embracing change and adaptive learning on both the corporate and individual levels as opposed to "frozen state" approaches.

Figure 1: Focus areas in an AI quality assurance master plan, including internal and external drivers.

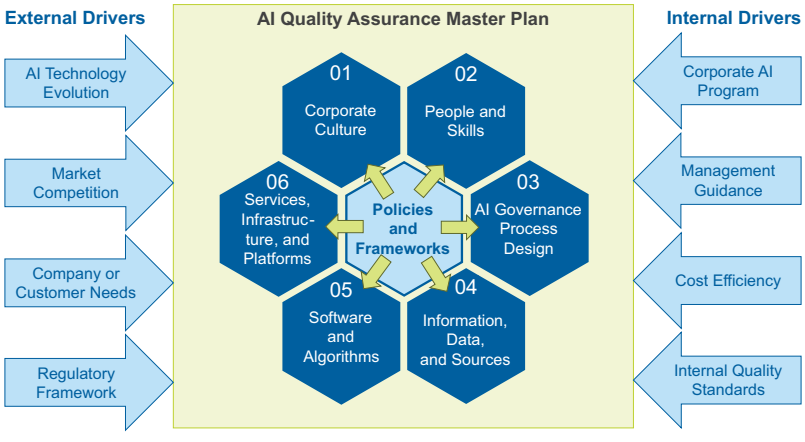
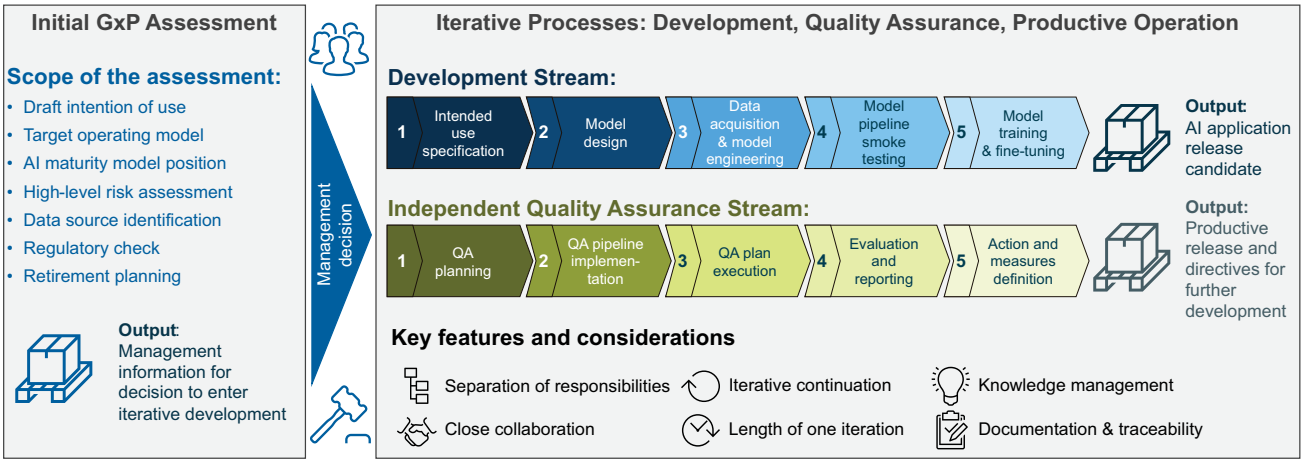


Figure 2: Initial GxP assessment and iterative processes that should govern the AI solution life cycle.



- People and skills: Effective AI development and quality assurance require a large set of stakeholders—typically organized in different business units—who need to be aligned in a structured manner to foster a collaborative environment.
- AI governance process design: AI solutions are inherently evolutionary in their nature. Their purpose is to continuously learn from new insights and data. Therefore, the process design must support this iterative nature and simultaneously ensure the quality required in a GxP-relevant context.
- Information, data, and sources: These assets are the fuel for every AI solution, and they need to be carefully evaluated with regard to quality standards.
- Software and algorithms: AI-featured algorithms come in many forms, from self-developed to freely available software. In addition to the choice of the actual AI model, the implementation is important to consider, in particular given the complex nature of many AI algorithms (e.g., deep neural networks).
- Services, infrastructure, and platforms: AI solutions are typically accompanied by large amounts of data. Real-time performance hardware and infrastructure are required for the AI solution to run during production.

This article covers (see Figure 2):

- Overview of the process design: In this section, we present an overview of the processes that should accompany the life cycle of an AI application.
- Initial GxP assessment phase: As a first step, we propose a structured preliminary analysis, which should assess whether an AI solution should be introduced in a specific context.
- Iterative process design: Reflecting the evolutionary nature of AI solutions, we propose a process design that develops iteratively. Our step-by-step approach includes quality assurance activities and clearly delineates responsibilities for all those involved in the process.

OVERVIEW OF THE PROCESS DESIGN

The AI governance process design begins by asking the following question: Where should AI be applied in the product life cycle so it leads to enhancements of the existing quality management system and ensures appropriate governance and risk management related to the application of AI in a regulated environment? To answer this question, consider that AI applications are evolutionary by their very nature:

- As new data are generated and collected, the AI solution should adapt to new situations or refine former results for continuous improvement.
- As technology evolves, and new AI algorithms become feasible, new modeling opportunities arise that may provide more value from a benefit or risk perspective.
- As AI solutions build incremental understanding for the use cases and the best modeling alternatives, new use cases might be identified in the course of the AI application's life cycle.
- As the regulatory framework and interpretation changes, new requirements may be imposed that provide new opportunities for applying AI solutions.

With the interconnection of AI, existing quality management systems, and classical computerized systems in mind, the proposed high-level AI governance process design consists of three dedicated phases:

1. Project initiation and initial GxP assessment should provide a valid entry point for the actual development of the solution, guided by a clear management decision.
2. Development, quality assurance, and productive operation should be conducted via an iterative, yet tightly controlled, approach and reflect the evolutionary nature of AI solutions.
3. Product discontinuation and retirement should be considered, even at the initiation of the project, especially in an AI context since the data characteristics—and therefore the results—may drastically change when the solution is phased out.

Figure 3: Overview of AI application fields in the pharmaceutical production process and value chain.

INITIAL GxP ASSESSMENT PHASE

AI systems that will function in the GxP area, such as inspection systems in production or systems processing pharmacovigilance data, need to comply with the classical pharmaceutical models for a quality management system as proposed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guideline Q10: Pharmaceutical Quality System [7].

This model for a pharmaceutical quality system can be implemented throughout the different stages of a product life cycle, from pharmaceutical development to technology transfer to commercial manufacturing, until product discontinuation (see Figure 3).

The elements of the pharmaceutical quality management system include the following: Process performance and product quality monitoring system; corrective action and preventive action (CAPA) system; change management system; and management review of process performance and product quality.

Since substantial resources may be involved in the development of an AI solution, an informed management decision should be made regarding the general feasibility of the AI solution. To facilitate the decision-making process, formal assessments for planned AI use cases supporting the quality management system elements within the life cycle phases should be implemented to answer the following key questions:

- Is the implementation of a planned AI use case permitted?
- Are there any external requirements (e.g., regulatory, ethical, legal, or customer related) that prohibit the use of AI?
- Are there any internal requirements (e.g., business sector, organizational) that prohibit the use of AI?
- Is an AI approach suitable for the specific use case?
- Is the impact on processes, functionality, and data integrity fully transparent?
- Are risk assessments, including acceptable risk mitigation measures, applicable?
- Can we expect data of sufficient quality (for development and during production) for the AI system to operate in production?

To answer these questions, the following are required: a draft of the intention of use, the operational design regarding human oversight, a high-level risk assessment, a regulatory check of whether an AI solution is actually permitted to be applied in this context, and the identification of suitable data sources.

All relevant stakeholders should be included in the assessment to consider all aspects of a planned AI use case; at a minimum, process owners (business), system owners (IT), and quality delegates should be represented in the evaluation. From a management point of view, suitable personnel should be identified who will be in charge of development, quality assurance, and productive operation. At this stage, the retirement approach of the AI solution should be drafted ("exit strategy").

ITERATIVE PROCESS DESIGN

As part of the iterative process design, we suggest two streams: one focusing on development activities, and the other focusing on stringent quality assurance. However, these two streams are closely interlinked and provide feedback as well as defined artifacts. At the same time, this design provides for the separation of duties to ensure a four-eye principle for the development of AI solutions in GxP-relevant contexts. In this case, four-eye principle means that any AI application may go productive only if at least two independent parties, as in the development and the QA stream, have assessed its quality. Further layers of control would be added with management involvement and potentially additional parties such as external auditors.

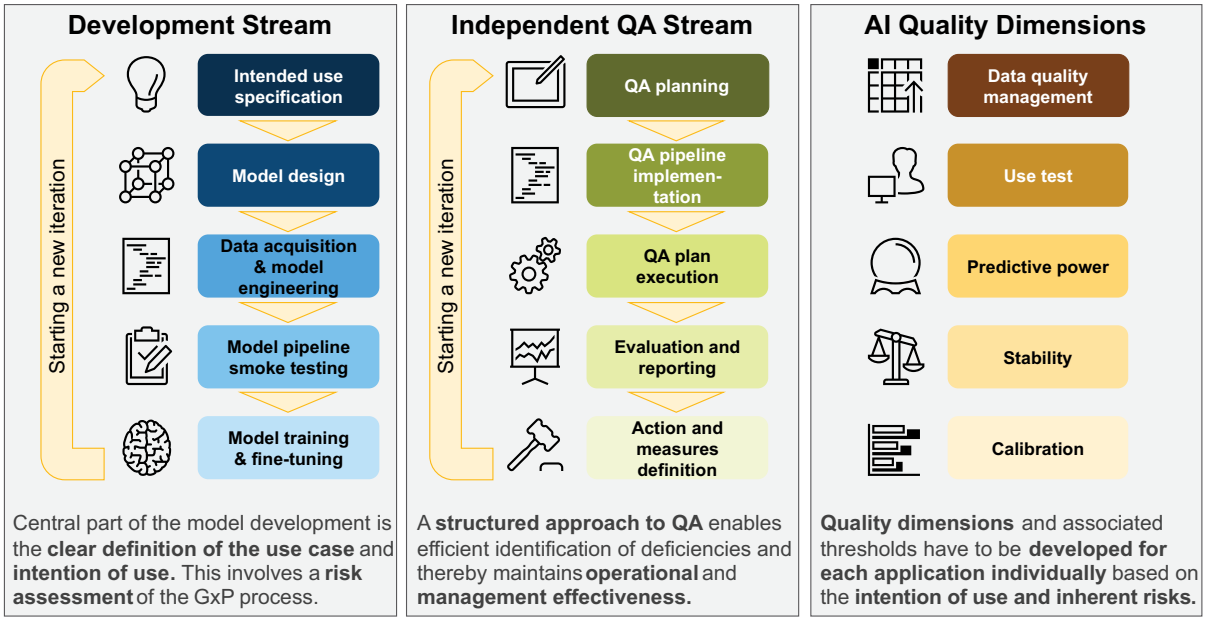
The separation of duties between the development stream and the independent quality assurance stream of the intended use can be achieved using one of the following means:

- Organizational: Separation of development and the involvement of independent quality assurance.
- Procedural: Separate responsibilities among development and quality assurance within an integrated process, but with different process owners in person.

These approaches should ensure that the quality dimensions that are required for safe and effective productive use are met. These concepts are summarized in Figure 4.

An iteration leads to a defined version of the AI solution and covers both the development and the quality assurance streams.

Figure 4: Iterative processes and the AI quality dimensions.



An iteration may last as long as the use case requires. The following aspects should be considered:

- Longer iterations involve more risk for the current implementation phase and increase the potential for friction between the development and the independent quality assurance streams.
- The lengths of the iterations may change during the lifetime of the application as long as the two streams are appropriately synchronized.
- Relevant input for the length of the iteration should depend on the speed of new data and the input generated by customers, patients, or stakeholders, which originates from post-marketing surveillance activities.

Development Stream

The development cycle involves all activities needed to produce an AI release candidate, i.e., a packaged solution that can be deployed on a suitable infrastructure and that will be assessed for fitness for production along with required documentation. Multiple cycles could be applied during the lifetime of the AI application, which means that there are two general types of development cycles:

1. Initial development iteration: Usually, only historical data and a draft for the intention of use are available in the first development cycle. Also, the development should be completely decoupled from production in order to mitigate any risks on the actual GxP-relevant process.
2. Subsequent iterations: Later development cycles profit from a more refined intention of use and risk assessment as a basis for further development. In addition, these cycles may react to findings generated during independent quality assurance and post-marketing monitoring in case a version of the AI system is already in operation. The development activities should be conducted in a manner that mitigates any risks on the actual productive process.

However, the following structure meets the needs of both the initial and subsequent cycles by following a five-step approach:

1. Intended use specification: In the beginning of every cycle, it should be specified what optimization targets the AI solution should achieve. In addition, the specific environment (e.g., physical environment, users, and other stakeholders) in which the application will operate should be specified. The initial analysis is concluded by a stringent risk assessment regarding AI-specific risks and other risks related to the application. The intended use may be expanded or altered in each cycle while maintaining an overview of the application's target and its inherent risks.
2. Model design: Given the intended use, a suitable modeling strategy should be chosen from clustering analysis, binary decisions, or probability estimates. Suitable data sources and use-case-driven feature definitions may be created. With a use-case-driven approach, all techniques to design features from their expected behavior within the data set or the classifier without necessarily doing a quantitative analysis at this stage of the process are in place. Hence, the expert expectation is formulated, which is assessed and augmented based on the data-driven features in the following steps. As a result of this phase, a functional model specification is created that shows how the AI solution is designed to solve the problem imposed by the intention of use.
3. Data acquisition and model engineering: This step involves all

activities necessary to turn the model design into a working AI system in a development environment and potentially a test environment. These activities typically include the following:

- The provision, preparation, and quality assurance of selected data per the model design. Data might need to be augmented or imputed as justified by the use case.
- The implementation and packaging of the actual AI software and its adjacent non-AI components.
- The implementation of deployment routines that deliver the AI system to a suitable infrastructure.

4. Model pipeline smoke testing: In this step, the model mechanics should be quality assured. Crucial points are data interfaces (e.g., input data or parameters) where the adherence to the data and model conventions should be checked (e.g., positive or negative weights). Furthermore, the non-AI elements of the solution should be verified using classical computerized software validation.
5. Model training and fine-tuning: Once the model can be applied to the data, the model should be trained on a defined training set. Based on the first results, the model may be fine-tuned, and further features may be developed while reaching a set of suitable models for productive use and challenger models (i.e., models that are running parallel to the productive model to provide ideas for further improvements). In order to measure the improvement during fine-tuning, the development team will implement suitable quality measures to reach the optimum model given the intention of use. The result of this step is a set of potentially (i.e., from a technical point of view) releasable models, ready for subsequent quality assurance activities.

Independent Quality Assurance Stream

The independent quality assurance stream should be applied as often as the development stream runs. With potential additional runs (e.g., for regular or ad hoc quality inspection), this process should be streamlined as much as possible. The five-step approach mimics the development cycle:

QA planning

The scope of analysis—based on the intention of use and identified risks—should be determined, involving acceptable qualitative and quantitative outcomes and measures. In addition, specific action should be formulated if thresholds or limits are not met as guidance for the further development of the AI solution.

QA pipeline implementation

Since the quality assurance should be run often in this iterative setting, analyses and quality assurance steps should be automated to the extent possible. Although most of the quality assurance activities should be automated, a process may start by relying more on manual steps if the integrity of the quality assurance outcomes are protected. This quality assurance pipeline should be tested with regards to good software development practices, including performance summaries and management reports.

> AI systems that will function in the GxP area need to comply with the classical pharmaceutical models for a quality management system.

Finally, more organizational and qualitative facets of the quality assurance exercise should be aligned (e.g., subject matter expert or user interviews and expert panels) to allow for a smooth operational process.

QA plan execution

Once the AI application's release candidate is handed over from the development stream to the independent QA stream, the release candidate is deployed on the QA team's infrastructure and suitable test data is delivered to their environment. The QA team is, in general, responsible for the test data that is delivered, especially with regard to the representativeness of the data vis-a-vis the intention of use. However, as the provisioning of test data may require complex data pipelines, the QA team may leverage existing data pipelines that were developed during the development stream as long as they retain full responsibility for the delivered data. Now, the quantitative quality assurance analysis is executed. Furthermore, ad hoc and qualitative analyses are conducted, and the results collected. An important aspect of these exercises is a traceable environment to allow for a post-marketing audit; in particular, all quality assurance results need to be reproducible in reasonable time. The time frame in which the results may be reproduced may vary with the use case. As a general guidance, the timespan of the original QA exercise runtime plus an additional setup time up to several days should be justifiable. In our view, more important is the exact reproducibility of the results that were obtained at the original run rather than the time to retrieve the replica.

Evaluation and reporting

The quality assurance results are investigated, and potential deficiencies are identified given the thresholds and targets in the first step. The results are prepared for high-level decision-making, which involves management recommendations and actionable measures, ranging from the deployment decision of the release

candidate to specific areas of improvement as guidance for the next implementation cycle.

Action and measures definition

On an appropriate management level, a decision is made whether to continue with the AI solution. Crucial input for those decisions involves the quality assurance results and the functionality-oriented intention of use and risk assessment. The action definition may involve adjustments to the quality assurance framework itself (e.g., measures and quality assurance approach or thresholds). Although actions guide the further development of the AI solution, measures are designed to mitigate risks that may be identified during the development and quality assurance of the model, potentially based on post-marketing information.

A particularly important aspect in the context of GxP is CAPAs. Because CAPAs focus on clear deficiencies of the release candidate under investigation, measures of this kind should have priority against the continuous improvement of the model. CAPAs may be defined based on deviations in the overall quality assurance outcomes of the model (e.g., its predictability or any potential in bias) or from available single incidents reported via post-marketing studies or other post-marketing information.

INTENTION OF USE, RISK ASSESSMENT, AND AI QUALITY DIMENSIONS

The core of each AI application is the intention of use (i.e., what the application should achieve). By safeguarding the application of the solution, a risk assessment identifies potential risks before release and directs the development and quality assurance activities to mitigate those risks while providing the benefits specified in the intention of use. In the following subsections, we show how these items are interlinked and illustrate the application with specific examples in GxP-relevant contexts.

The following overview shows how the intention of use specification, the AI-specific risk assessment, and quality dimensions can be identified in a structured manner and what can be concluded from these steps. These activities, as well as the actual monitoring of the performance metrics themselves, should be seen as an ongoing process, since new signals originating from post-marketing surveillance or follow-up studies after adopted in production may shift the AI application's intention of use, the risk profile, and the quality measurement. Also, this analysis may provide input for the positioning in the maturity space for the target operating control model design of the AI system.

The intention of use should clearly communicate the purpose of the AI solution:

- What the application should achieve and in which environment the application should operate (physical environment, users, patient groups, and other stakeholders).
- What alternatives exist and why an AI solution might provide additional benefits.
- The AI-specific risk assessment should reflect the stochastic nature of the AI application in addition to classical risks:
  - What physical, legal, or budgetary impact might arise from misclassifications or inaccurate results to the patient, the user, the organization, or others? How much would this distort acceptance and trust in the data and solution?
  - What risks might threaten the AI development and quality assurance iteration or stream as a whole?
- Quality dimensions should be tailored to the AI solution such that identified risks are effectively and communicably monitored; and suitable thresholds are defined that capture the state-of-the-art expectations to the AI solutions outcomes and alternative means for fulfilling the intended use (if available).
- Measures should be defined based on the risk assessment to mitigate the risks that were identified in the risk assessment or given the outcomes of the quality dimensions. Measures should be proportionate with regard to the risks involved and the human oversight involved in the operation of the AI solution; the choice of human control as a mitigation strategy is an important factor to shield against AI errors and to foster trust into the application of the AI solution. A clear rationale—qualitative and/or quantitative—should be provided that shows the suitability of said measures, focusing on risk mitigation.

The regular evaluation as per the quality assurance stream should provide a decision basis for the subsequent development activities and measures. Regarding the release of a new version, an AI solution release candidate passes the quality assurance check if risks are mitigated according to the quality dimension standards, and if it can be demonstrated that the model is the best choice given the current state-of-the-art data, development, and quality assurance.

The choice of measures, rigor, and transparency implemented depends on the risk assessment of the AI application. The same risk assessment methodology should be applied for all AI systems within the corporation and follow defined, clear, and sensible criteria leveraging already implemented risk assessment processes. The impact on risk toward patient/consumer safety, product quality, and data integrity will drive the quality assurance of the AI system and regulatory burden. It should be noted that from a regulator's perspective, a risk-based approach is also desired, and inspections focus on critical systems with an impact on public health. An established strategy is the two-stage risk assessment that involves (a) an initial risk assessment and determination of the system impact (GxP applicability determination) and (b) functional risk assessment on the user requirements and system functionality as described in the introductory part of the AI governance process design.

To provide a structure for measuring the AI application's performance with respect to the intention of use and the risk assessment, five quality dimensions can be used to validate the stochastic nature of AI applications:

1. Data quality management: Does the productive data adhere to data expectations? Is the data in the training set representative of productive use?

2. Use test: Has the system been used according to its intention, for its target group or target operation, and according to the specified user–machine interaction?
3. Predictive power: Has the system been able to effectively predict the desired outcome based on its input?
4. Stability and robustness: Does the model provide consistent outputs with regard to the evolution in time of input data and the model itself?
5. Calibration: Does the model exhibit biases on a global level or for particular, undesired stratifications?

Although all quality dimensions are relevant to AI applications in general, the actual focus and selected measures can be tailored to the intention of use and the risk assessment. This means that measures and thresholds of quality dimensions should be chosen in a risk-based manner, reflecting the most critical aspects of the AI solution as per risk assessment. Also, priorities and trade-offs have to be chosen in this regard; for example, the predictive power and the stability commonly result in conflicts that have to be resolved based on stakeholder (i.e., users, patients) expectations and the risk appetite in line with the corporation's AI strategy.

CONCLUSION

While AI- and machine-learning-specific regulations are currently under development, more detailed guidance is needed to turn these regulations into AI solutions that can be applied in GxP-relevant contexts. With its stepwise process design, the AI governance and quality assurance framework ensures both full and auditable process control and agility, which are necessary to successfully benefit from these new technologies and unlock their full potential. Specific tasks and responsibilities are encapsulated in a structured manner but are still flexible enough to be applied to a specific context of an AI solution. In further publications, we will elaborate on other focus areas of our AI governance and quality assurance framework, with further details regarding both technical considerations (e.g., IT security) and organizational challenges when introducing AI development at a corporation. We believe that the approach described in this article has considerable potential for application in other life science industries.

The AI governance and quality assurance framework ensures both full and auditable process control and agility.

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Acknowledgments

The authors thank the ISPE GAMP® D/A/CH Working Group on AI Validation, led by Robert Hahnraths and Joerg Stueben, for their assistance in the preparation of this article, and Markus Kaufmann and Rolf Blumenthal for their review.

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INTRODUCTION
to Steam Quality and Testing

By Nissan Cohen, Nicholas Haycocks, Jeremy Miller, FIET, FinstR, Derek Mullins, and Keith Shuttleworth

Steam is the most powerful and effective thermal energy transfer fluid, and its use continues to grow in process industries around the world. However, there is very little written about the commissioning and qualification of pharmaceutical pure steam systems in GMP regulations or regulatory guidance. This article provides the background and science behind the steam quality tests and proposes a risk-based approach to the routine monitoring of steam quality for a system providing steam to all pharmaceutical applications/autoclaves.

Ask anyone about steam engineering, and they will likely think of lumbering locomotives and traction engines from a bygone era. The more well informed will know about the role of steam in the Rankine cycle and power generation. But few will know that steam is used in process industries worldwide because it is the most powerful and effective thermal energy transfer fluid. It remains the most powerful and efficient way of controllably transferring heat to the many processes and utilities around a plant. For that reason, in a modern pharmaceutical plant, steam is an essential tool.

A steam pipe can transfer approximately four times the amount of thermal energy as an electrical cable with an equivalent diameter (Figure 1). Generating steam centrally at moderate pressures allows the use of relatively small pipes, before the pressure and temperature are reduced to suit the process or application.

For saturated steam, there is a defined physical relationship between pressure and temperature that supports good temperature control and ensures that any process is kept within temperature limits.

Because many critical processes in the pharmaceutical industry use steam in direct contact with the product or product contact surfaces (such as during sterilization), it is essential that the use of steam meets regulatory expectations.

The latent heat that steam releases when it condenses into liquid is the greatest of any of the common fluids available. Steam latent heat is relatively constant over a broad pressure range, giving rise to a condensing heat transfer coefficient of between 4,000 and 15,000 w/(m^{2}K) [2]. It is this combination of controllable temperature and high heat flux that makes steam rapid in response and a highly effective thermal tool.

STEAM-DRIVEN APPLICATIONS

Various processes in the pharmaceutical industry use steam, with different properties depending on the process requirements and the potential risk to product quality. Pharmaceutical steam is classified into three types:

Figure 1: Thermal energy capacity: steam versus electricity [1].

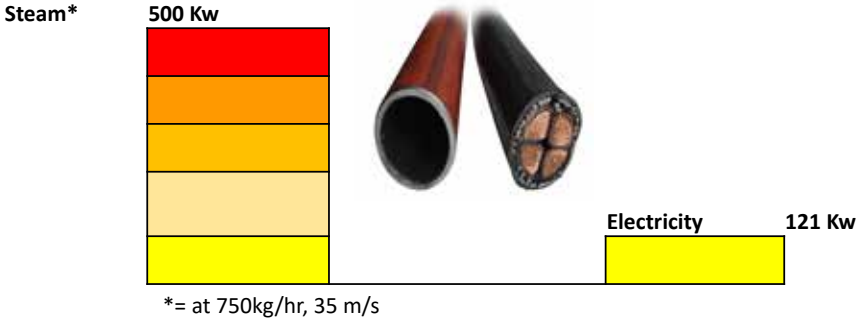
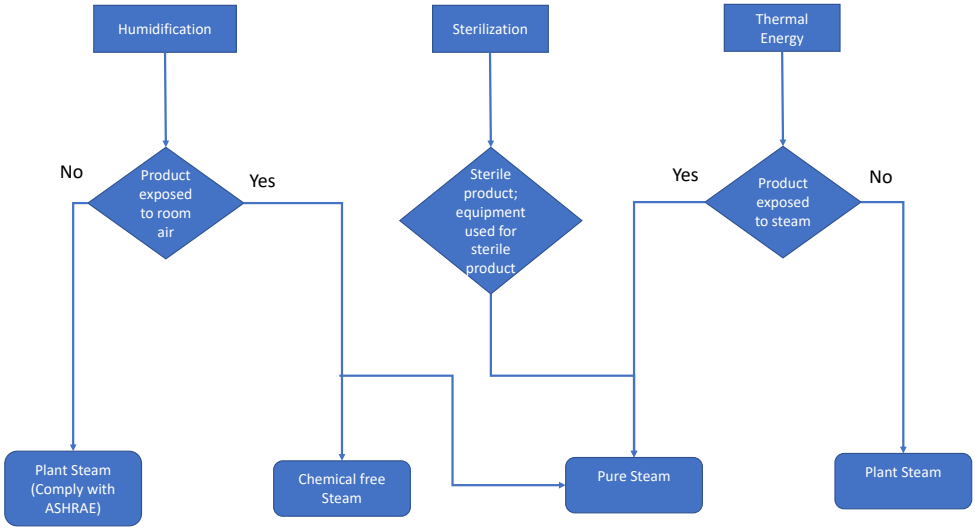


Figure 2: Steam application decision tree.



- Plant (utility boiler produced) steam
- Chemical-free (non-utility boiler produced) steam
- Pure (non-utility boiler produced) steam

Figure 2 shows typical applications for the different types of steam.

Plant Steam

Plant steam is used in applications that involve no direct contact between the steam and the product or product contact equipment. It is produced from potable water fed into an industrial-type boiler, where additives are used to raise the pH to 9.5–10.5 to protect carbon steel equipment from corrosion.

It is used as a heat source for non-critical and cGMP heat exchangers for heating (frost protection) coils in heating, ventilation, and air conditioning (HVAC) applications, as well as in critical applications such as water for injection (WFI) production via heat exchangers. It can also be used to sanitize non-product contact equipment or for the biological destruction of solid or liquid wastes in equipment sometimes known as "kill tanks."

Chemical-Free Steam

Chemical-free steam is similar to plant steam in that is generally used in non-direct contact applications. The key difference is, as the name suggests, that it is produced from pretreated (usually softened) water, meaning it has not been treated with volatile or non-food-grade boiler additives.

Primarily reserved for humidification and nonsterile product sanitization or bioburden control, chemical-free steam is also used for non-critical steps in the manufacture of active pharmaceutical ingredients (APIs) involving no contact with the product. Humidification for HVAC pharmaceutical systems (usually provided prior to the system high efficiency particulate air [HEPA] filter) and bioburden control of early-stage manufacturing equipment both fall into this category. Chemical-free steam provides an acceptable level of purity because any added impurities will be removed in subsequent procedures.

Pure Steam

Pure steam, otherwise known as "clean" steam, is generated from treated water that meets applicable drinking water regulations, USP Purified or WFI classifications, and is free of any additives (amines and hydrazines). It is used for thermal disinfection or sterilization processes as well as equipment sterilization processes (e.g., freeze dryers, process equipment, and pipework) and sterilization using an autoclave or stopper processor.

PURE STEAM QUALITY

The feedwater for a pure steam system must meet local potable water standards. The steam quality, measured as condensate, must meet the relevant specifications for WFI, excluding the microbiological requirements, but including endotoxins. There are national standards and guidelines defining the engineering specifications for steam generation plant and distribution systems, such as those from the American Society of Mechanical Engineers (ASME) [3]. and ISPE's Baseline Guide for Water and Steam Systems version 3 [4]. These will include material specifications, dimensions/tolerances, surface finish, material joining, and quality assurance procedures.

There are also specifications established through European Standard EN 285:2015, Sterilization. Steam Sterilizers. Large Sterilizers [5], for pure steam quality when used for sterilizers:

- Supply steam must have a dryness value of no less than 0.95.
- Obtain no more than 3.5 ml of gases per 100 ml of condensate.
- Superheat to be less than 25°C when expanded to atmospheric pressure.

Table 1: Steam quality testing standard documents.

Steam Quality Testing Standard	Document Title	Notes
ANSI/AAMI ST79: 2017 [9]	Comprehensive guide to steam sterilization and sterility assurance in health care facilities	Higher requirement for steam dryness compared to EN 285
EN 285: 2015 [5]	Sterilization. Steam sterilizers. Large sterilizers	Covers Europe and the UK
Parenteral Drug Association (PDA) Technical Report TR1 [10]	Validation of moist heat sterilization processes; Cycle design, development, qualification and ongoing control	TR 61- Steam in Place does not have any relevant content
Parenteral Drug Association (PDA) Technical Report TR48 [11]	Moist heat sterilizer systems: Design, commissioning, qualification and maintenance	
USP 43–NF 38 [12]	Monograph for Pure Steam	The level of steam saturation or dryness, and the amount of NCGs are to be determined by the pure steam application

Table 2: EN 285: 2021 requirements.

Parameter	Steam Dryness Value	NCGs	Superheat
EN 285 2015	> 0.95 w/w	≤ 3.5 ml/100 ml	> 25

w/w = weight per unit of weight.

The requirement for steam quality tests has long been a topic of discussion. Some questions arise from a lack of understanding of the origins of steam testing and how the principles apply to different sterilizer load types: non-porous and porous. Here we aim to explain these quality parameters, and their impact.

The heat penetration for a non-porous load comes from the heat transfer to the item through the outer surfaces; usually the challenge is that in the time taken to heat up the thermal mass, any steam superheat would be dissipated by the mass, and the impact of non-condensable gases (NCGs) would be limited. A porous load, like a filter or a garment, presents a different challenge. In this case, NCGs could create a problem by lodging in the load and acting as an insulator, preventing heat transfer to the inner parts of a load item.

Steam Testing

In the mid-1970s, the UK National Health Service was experiencing a significant number of failures in porous load and equipment sterilization cycles, incurring considerable costs and jeopardizing patient safety. Keith Oates, from the Scientific and Technical branch of the Department of Health and Social Security, was charged with resolving this issue. He discovered that the problem was poor steam quality, for which he developed a means of simulating variation in the quality parameters and supporting tests to measure the levels of the quality parameters [6]. His work was incorporated into Hospital Technical Memorandum (HTM) 10, published in 1980 [7], as diagnostic tools that included the test methodology for determining dryness and NCGs.

HTM 10 was replaced by HTM 2010 [8] in 1994: Oates was one of the principal authors and the Work Group Convener for the original version of EN 285: 1996 [5], which included the steam quality tests, with the associated test methods and acceptance criteria.

With the publication of HTM 2010 [8], the Medicines and Healthcare Products Regulatory Agency (MHRA; MCA at the time) recognized that the issues impacting sterilizers in hospitals would have a similar impact on sterilization in the pharmaceutical industry. MHRA began to apply the same steam quality criteria when inspecting manufacturing companies domestically, as well as in their role as European Medicines Agency (EMA) inspectors. Although HTM 2010 [8] may have originally been cited as a reference, this practice appeared to cease on the publication of EN 285: 1996 [5]. (EN 285 was updated in 2015 and 2021.)

Steam testing and the introduction of specific criteria became accepted; both are now a standard practice. Currently the standards for steam quality testing are defined in a number of documents, shown in Table 1; however, each differs slightly.

The pharmaceutical/biotechnology industry typically references EN 285: 2015 [5], which has the requirements listed in Table 2.

For laboratory autoclaves, >0.90 w/w is considered acceptable.

EN 285 [5] and HTM 2010 [8] refer to dryness as a unitless value. The term w/w is properly used when describing the dryness fraction. It should be noted that the NCG limit has changed in EN 285: 2015 [5] and is no longer represented by a percentage.

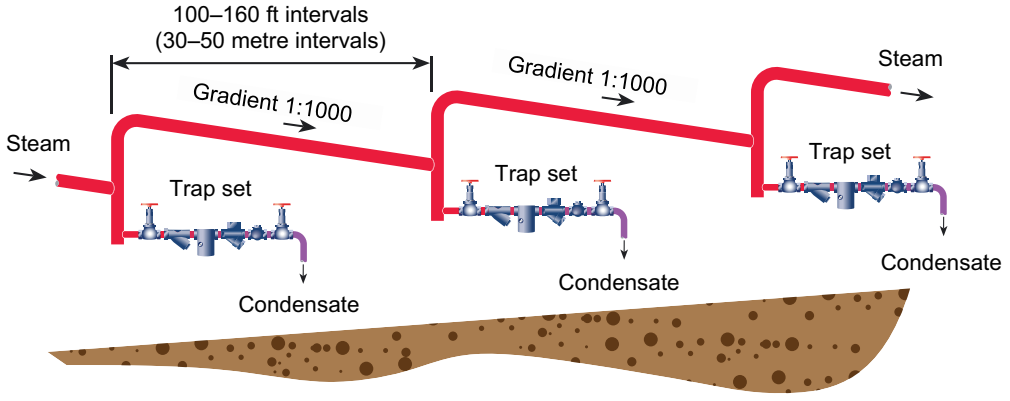
Various aspects of the system design and installation impact the system's ability to meet the requirements; therefore, it is imperative to design and install systems properly. Each quality requirement is discussed further in the next section.

STEAM DRYNESS

Steam dryness is important, because wet steam can cause wet loads, with consequent risks to sterility if products are stored wet. Wet steam also has less enthalpy than dry steam, so a greater quantity is required to provide the equivalent heat energy. Moisture droplets can also damage pipework and valves.

Dryness value is primarily a function of the distribution system design/demand at the time of testing. Testing for dryness around the steam distribution system at critical points is a valuable way of confirming that a steam system has a competent design and is being well maintained.

Figure 3: Design requirements for a steam distribution system.



Dryness Fraction

The term "dryness fraction" implies an absolute and exact mathematical measurement of the mass of water contained in a given mass of steam. The term "dryness value," however, is used to describe the amount of moisture present based on the EN 285/HTM 2010 [5/8] methodology, which is not exact.

A well-designed steam generator produces steam with a dryness fraction of 1. Many generators will include or recommend that a separator is fitted immediately downstream of the generator outlet to ensure such a dryness fraction is achieved.

By definition, 100% dry saturated steam with a dryness fraction of 1 is steam that is at its condensing point and, as such, in a transient condition. Any heat loss will result in condensate being generated and the steam becoming wetter. Maintaining steam in a condition that is as dry as possible requires good engineering design and practice throughout the steam distribution system.

Condensate

As soon as the steam leaves the generator, it is distributed through a metallic pipework system that is kept hot by the heat gain due to the steam condensing on the walls of the distribution system. The pipework is kept at a temperature close to the steam temperature, though there is a small temperature loss due to the boundary layer. Some of the condensate from the pipe walls will be picked up by the steam being transported through the system. There will be more condensation if the insulation is poor or damaged, and more condensate will be carried by the steam, if the system has a poor fall or slope, or if it is inadequately drained. If the steam consumption increases, there will be less condensate proportionally. Typically, steam systems have a small rivulet of condensate which is removed by steam traps placed throughout the piping system.

A well-designed distribution system has a slope of not less than 100 mm per 10 meters of pipe (1:100) in the direction of steam flow, with steam traps installed in pockets at 30- to 50-meter (90- to 150-feet) intervals to remove any condensate that has formed. Usually the condensate, which is small in volume, flows at the bottom of the pipe. This small bead or rivulet is removed from the system via the condensate trap, which is installed in a small tee off the bottom of the pipe (Figure 3). If steam headers are used, they should be installed with the correct drainage angle to a steam trap to prevent any pooling of condensate.

It is good engineering practice to fit a separator just before the connection to the sterilizer to ensure as much condensate is removed as possible. Condensate in any pools can be picked up by higher steam velocities as they occur through the sterilizer cycle. Additionally, an inline separator can remove any entrained water/condensate. Suspended water droplets are impinged on a series of baffles before flowing via gravity into a drainable outlet trap. Separators installed immediately before or after the valve are a simple but effective solution and typically remove more than 99% of condensate.

Test Sample

Per EN 285 [5], the quality test sample should be taken from the center of the pipe and should be representative of the quality of the steam being used in the system. However, it is not representative of the overall steam quality at that point, and as such it is known as the dryness value. Overall steam quality can be measured by using a static mixer to mix all the condensate together with the steam and measuring close to the mixing point.

In this case, a sample will be representative of the overall system steam condition at that sampling point and is known as dryness fraction. With well-functioning steam traps and separators, condensate at the bottom of the pipe will be removed, so a measurement from the center of the pipe may be considered representative.

Dryness as a Diagnostic

Accurately measuring steam dryness fraction can be a very useful diagnostic of the overall health of a steam system. A low fraction value can have a number of causes:

- Damaged/degraded insulation on the steam distribution system
- Inadequate drainage of the distribution system due to insufficient fall/slope
- Pipe sagging
- Dead legs (sections of piping that do not allow steam to flow)
- Steam velocity (demand)
- Insufficient drainage slope on steam headers
- Malfunctioning steam traps/separators, preventing effective condensate removal
- Inadequate/poorly located steam traps, preventing effective condensate removal
- Clogged steam filters (if they are used), causing an unusually high pressure drop that reduces steam flow
- Poor steam generator maintenance or operation

Impact of a Low Dryness Fraction

Wet steam can cause wet loads with consequent risks to sterility if products are stored wet. Wet steam has less enthalpy than dry, so a greater quantity is required to provide the equivalent heat energy. Moisture droplets can also damage pipework and valves.

Dryness value is primarily a function of the distribution system design/demand at the time of testing. Testing for dryness around the steam distribution system at critical points is a valuable way of confirming that a steam system has a competent design and is being well maintained.

Commissioning, Testing, and Monitoring

Testing is required for steam sterilizers. If the pipework design is similar in terms of the design (length of pipe run/fall, steam trap types and location) per sterilizer connection, then a reading on the index run is all that is necessary. But as the pipework typically varies for each connection, each autoclave connection is typically tested for dryness value during commissioning/qualification.

NON-CONDENSABLE GASES

Non-condensable gases (NCGs) are gases that are entrained in the steam during generation. Air and other NCGs act as an insulator and should therefore be minimized in pharmaceutical steam systems. Such impurities offer a highly effective barrier to steam penetration and heat transfer, resulting in a reduced load temperature or absence of moisture at the interface with the load. With porous load (such as gowns), the gas may prevent penetration of the load, and could mean lower temperatures for system components or process equipment, potentially leading to incomplete sterilization.

Thermostatic steam traps are placed within the distribution system in positions where air is prone to collect, such as the terminal points of the main and large branches of the steam header. Working on the basis that air is heavier than steam in the distribution system, the traps separate and remove the NCGs to improve the quality of the steam. Although this is true under static conditions, when steam is flowing, NCGs will travel in the direction of flow. Good practice is to also fit air vents at the end of branches and at system high points, because excessive levels of air may slow down the discharge of condensate. Excess water from subcooled condensate can cause insufficient sterilization temperatures.

NCGs are a function of the feedwater quality and the effectiveness of any degassing system. Whether through preheating feedwater and allowing it to vent, or through the use of a separator on the generator, the levels will vary depending on feedwater quality and on the system state and flow rate. It should also be noted that levels may be higher after a period of nonuse (e.g., overnight). Even small amounts of NCGs can accumulate in the steam distribution system and can subsequently be pushed out as a large volume on startup. This is mitigated in a well-designed system by ensuring the steam distribution system has proper air venting arrangements.

For a steam in place (SIP) system (this would include a tank or lyophilizer), the efficacy of the design for the vents and system drainage are confirmed during commissioning. The location of the cold spot is typically identified and used for ongoing monitoring or periodic performance assessment. This is considered adequate control and it is not necessary to confirm NCG levels for a steam system feeding an SIP system.

High NCG Value Causes

High NCG values can be caused by a number of conditions:

- Air ingress into the distribution system (e.g., if the system is shut down overnight, a vacuum will form as it cools potentially pulling in gases). A preoperational cycle on the autoclave can help manage this by flushing the system with steam.
- Inadequate venting of the steam distribution (or, in the case of SIP for a pipework system, inadequate venting of the pipework system).
- Inadequate de-aeration of the steam generator feedwater/degassing of the steam.
- Leaking glands on steam valves that allow the compressed air used for the valve actuators to enter into the steam system.

High NCG Impact

NCGs are released when the steam condenses. For an autoclave, this is at the interface with the load. Therefore, as more steam comes in to fill the void created by the change in volume created by steam condensing, more gas is released. The gas creates insulating pockets, preventing the surface of the load reaching temperature. Degasification either at or downstream of the steam generator can easily rid the system of NCGs. There has never been a product quality issue cited due to NCGs; however, NCGs will not appear in a root cause analysis if there is no knowledge or understanding of them. A typical scenario is where there is a failure(s) of a biological indicator (BI) and the response is to increase a sterilization time way in excess of that which should be necessary to inactivate the BI.

Commissioning, Testing, and Monitoring

NCGs are a function of the feedwater quality and particularly of temperature, system state and flow rate, the distribution system, venting design, and demand at the time of testing. Testing should

be completed for each sterilizer prior to qualification according to the procedure described in EN 285 [5] to confirm compliance and identify the worst-case location.

If any particular location (typically the index run) on a system consistently gives higher results than other points, then that single point should be verified annually, with all points verified if the result at that point is a failure, or marginal. (This strategy assumes that the original testing was carried out under normal operating conditions, so that the readings are typical.)

For an SIP system (this would include a tank or lyophilizer), commissioning typically maps the system to ensure that there is adequate venting and drainage to obtain uniform temperature distribution. The location of the cold spot is typically identified and used for ongoing monitoring or periodic performance assessment.

SUPERHEATED STEAM

Superheated steam is steam at a temperature higher than its vaporization point at the absolute pressure where the temperature is measured. It can therefore cool by a certain amount without changing state from a gas to a mixture of saturated vapor and liquid [1]. Superheated steam heats or cools convectively, whereas condensing steam heats directly by giving up its latent heat of vaporization. The heat transfer coefficient of the two mechanisms are very different.

As an example, we as humans breathe superheated air. At atmospheric pressure, the vaporization point for air is -194.35°C (-317.83°F). If the ambient air temperature is 20°C, then the air is superheated by 214.35°C (385.83°F) [1].

The heating convective coefficient at atmospheric pressure is likely to be in the range of 5-100 W/m²°C depending on steam velocity [2]. For steam condensing on a flat vertical surface, the value is 4,000°C to 11,300 W/m²°C. Superheated steam is therefore up to 11 times less effective than saturated steam as a heating agent. Although energy transfer plays no part in the F_0 (minimum time-temperature; see USP 1229.1) calculation, the rate of the transfer will affect the time required to reach the desired temperature. Fortunately, the amount of energy in superheat in a typical pharmaceutical plant steam system is small and easily dissipated by any wetness or heat transfer to the load requiring sterilization, resulting in saturated steam.

This can be illustrated with the following example: 100% dry (dryness fraction of 1) steam at 7.0 barg (101.5 psig) is passed through a pressure-reducing valve to reduce the pressure to 1.037 barg (15.05 psig). Such a pressure reduction is isenthalpic and an adiabatic calculation shows that the steam temperature after pressure reduction would be 149.76°C compared to a saturated temperature at 1.037 barg of 120.8°C—in other words, nearly 29°C of superheat. See Table 3 for other examples.

Although this might seem a large number, it represents less than 3% of the energy available from condensing the low-pressure steam in the sterilizer. In most installations, there is enough residual "wetness" to absorb this energy or sufficient "heat leakage" in the piping before the sterilizer to dissipate any superheat.

Table 3: Examples of superheat values.

Pressure/Dryness Fraction	
Before Pressure Drop	**After Pressure Drop**
5 BarA/0.95	3.2 BarA/0.96
5 BarA/0.98	3.2 BarA/0.99
5 BarA/0.95	2.1 BarA/0.97
5 BarA/0.98	2.1 BarA/1.0
5 BarA/0.98	1.0 BarA/at 10°C of superheat

Sterilization is achieved from the transfer of heat energy contained in saturated steam through condensation when the load temperature is raised sufficiently to inactivate bioburden loads, proteins, and other potential pathogens; sterilization occurs because of the presence of temperature and moisture. The energy level and rate of its transfer does not play a part in the sterilizing effect. Also, sterilization occurs in fluid loads in the absence of latent heat. Where the steam is superheated, the heat transfer during the initial cooling phase from the superheated steam temperature to the saturation temperature is not as efficient, as it is after the steam cools to the saturation temperature and where condensation occurs—the condensate improves the heat transfer raising the temperature, with the time at temperature sterilizing the material.

Potential Issues

Certain conditions may present a problem and must be watched for:

- Steam that is dry saturated (or close to it) can be subject to a significant pressure drop. Note: the risk increases with drier steam and larger pressure drops.
- Jacket temperature or pressure that is too high in an autoclave can effectively superheat the steam as it enters the autoclave.
- Steam flowing through a small orifice or a tight-radiused direction change between its source and the chamber or equipment can cause a large pressure reduction or steam velocity increase with no pipework to allow superheat to dissipate after the fitting/orifice (which could be a valve).
- System cannot maintain adequate pressure. For a simple system, steam is generated at a pressure slightly higher than that required for the users to allow for the pressure losses in the distribution system. For a large installation, the distribution pressure is typically significantly higher to ensure that there is adequate pressure to supply demand when multiple users call for steam at the same time. In this type of design, a pressure-reducing valve will be used on the supply to the use points.

Table 4: Proposed test requirements for commissioning/qualification and ongoing monitoring.

System Type	Commissioning/Qualification				Monitoring			
	Chem/ endotoxin	NCG	Dryness	SHT	Chem/ endotoxin*	NCG	Dryness	SHT
SIP	X	N/A	N/A	N/A	Q	N/A	N/A	N/A
LYO	X	N/A	N/A	N/A	Q	N/A	N/A	N/A
Autoclave	X	X	X	X	Q	Q*	A	N/A
Stopper processor	X	X	X	X	Q	Q*	A	N/A

A = annually; LYO = lyophilizer; N/A = not applicable; Q = quarterly; SHT = Superheat. Q* = quarterly initially until data are available to support reduced testing, assumes that the feedwater to the steam generator is routinely monitored.

Steam is one of the most effective mediums to transport thermal energy, but the control and potential impact of steam quality parameters should be understood.

- A poorly designed system will reduce pressure above a ratio (n) of 2:1 and not provide an adequate length of pipework for the steam to equilibrate before going to the control valve. Excessive pressure reduction can result in the steam generating significant superheat. With the more usual ratios, the quality of the steam will change (the process is isenthalpic [i.e., the enthalpy value remains constant], hence the changes in the steam quality).

Good design limits the stage pressure reduction per stage (not more than 2:1 per HTM 2010 Part 2 paragraph 7.20 [8]) and allows an adequate length of pipe for the steam to reach equilibrium before it is added to the autoclave chamber. Per HTM 2010 Part 2 [8], "where the supply pressure at the inlet to the sterilizer would exceed the maximum value specified by the manufacturer, a pressure-reducing system and separator should be fitted to the supply pipe at least 3 meters from the sterilizer. Heat loss from the section between the pressure-reducing system and the sterilizer will help prevent superheating."

Note that pure steam generators typically do not have the capability to produce superheated steam. The water is heated and evaporates, passing through a separator to prevent moisture droplets being carried over with the steam. The steam from the generatoris ideally dry saturated steam (with a dryness fraction of 1). The system is not designed to add heat to the steam or to create superheat.

Excess Superheat Impact

For a pharmaceutical system, the quality of the steam from the generator is generally consistent: superheat is a function of the distribution system design/flow rate.

For an SIP system (this would include a tank or lyophilizer), there is adequate pipework or metalwork for any superheat to be reduced. Due to the significant ratio of surface area to volume of the system, commissioning typically also temperature-maps the system to ensure there is adequate venting and drainage to obtain uniform temperature distribution; because of this, it is not considered necessary to measure superheat.

Commissioning, Testing, and Monitoring

For an autoclave, superheat levels can be tested during commissioning. Because the pipework to each system will vary slightly, each autoclave should be tested during commissioning. For an autoclave or SIP system, superheat is usually effectively monitored through the comparison of the temperature and pressure function in the automation. Alarm systems are in place to highlight a significant mismatch. The test regime proposed is shown in Table 4 (and supported by Table 5 in the Appendix that follows this article).

CONCLUSIONS

As the article explains, steam is one of the most effective mediums to transport thermal energy, but the control and potential impact of steam quality parameters should be understood. The design and maintenance of the steam distribution system is critical. An appropriate level of monitoring of the parameters should be used to confirm that the steam delivered is within the specified limits. Suggested testing is described in Table 4 (and supported by Table 5 in the Appendix that follows this article).

Appendix

Table 5: Pure steam sampling risk assessment.

Potential Failure Mode	Potential effect of failure	Severity	Potential Cause	Likelihood	Design controls	Operational Controls	Detection	Detection	Recommendation	Risk Level
Clean steam does not meet specification at point of use. (chemistry, endotoxin & physical properties)	Ineffective sterilization in steam sterilizers (autoclaves, stopper processers)	5	High non-condensable gases	3	Clean steam generator supplied with pre-heated water / fitted with degasser function	Monitoring of degassing critical parameter (temperature of feedwater or evaporator temperature in case of integral deaerator)	Commissioning / qualification testing of capability, and routine monitoring of evaporator or feedwater water temperature (depending on degasser type)	3	Initial performance testing at generation and supply to each sterilizer. Routine monitoring at worst-case point through annual testing at furthest autoclave or end of header.	Low
			Excess superheat	1	Piping design - limited pressure drop per stage with adequate pipework for fluid equilibration	Company SOPs require the steam supply to be qualified as part of the sterilizer commissioning / qualification.	Confirmation of superheat levels during commissioning / qualification		Initial performance testing at steam generator and supply to each sterilizer. Re verification if changes are made to local piping.	
		5	Low dryness (excess water droplets)	3	Generation system incorporates droplet separator. Distribution system incorporating drainage (falls), trapping, and specified levels of insulation, with a pocket and steam trap on the connection to the sterilizer.	Company SOPs require the steam supply to be qualified as part of the sterilizer commissioning / qualification. Annual system survey to detect changes or deterioration in distribution piping insulation, and confirm tagging is in place.	Confirmation of superheat levels during commissioning / qualification. Periodic testing at representative sample point	3	Testing at generation and supply to each sterilizer. Routine monitoring at worst-case point through annual testing at furthest autoclave or end of header.	Low
	Product contamination due to high bacterial endotoxin in steam	5	High endotoxin feedwater, carried over into steam	5	Generation system supplied with endotoxin controlled feedwater.	Company SOPs require the steam supply to be qualified as part of the sterilizer commissioning / qualification.	Quarterly sampling of feedwater for endotoxin.	1	Quarterly sampling of feedwater for endotoxin.	Low
		5	Ineffective separation and removal of endotoxins at generation	3	Multi stage impurity separation in clean steam generator, and blowdown to provide consistent feed quality.	Routine verification (annual) of blowdown volume	Routine monitoring of pure steam condensate.	3	Routine monitoring of pure steam condensate.	Low
	Product contamination due presence of organic carbon	5	High TOC in feedwater, carried over into steam	3	Generation unit supplied with TOC controlled feedwater.	Online TOC monitoring of feedwater	Alarm from online monitoring instrument	1	Continuous monitoring of the system feedwater.	Low
		5	Ineffective separation and removal at generation	3	Multi stage impurity separation in clean steam generator, and blowdown to remove impurities.	Routine verification (annual) of blowdown volume	Alarm from online monitoring instrument	1	Continuous monitoring of the generation system condensate, routine testing at representative sample point (pipework index (longest) run)	Low
	Product contamination due to high conductivity	5	High conductivity in feedwater, carried over into steam	5	Generation unit supplied with conductivity controlled feedwater.	Online conductivity monitoring of feedwater	Alarm from online monitoring instrument	1	Continuous monitoring of the system feedwater.	Low
		5	Ineffective separation and removal at generation	3	Multi stage impurity separation in clean steam generator, and blowdown to remove impurities.	Online conductivity monitoring of feedwater	Alarm from online monitoring instrument	3	Continuous monitoring of the generation system condensate, routine testing at representative sample point (pipework index (longest) run)	Low

SOP = standard operating procedures; TOC = total organic carbo

Table 6: Risk assessment scoring.

Rating	SEVERITY of the effect of failure (System/Equipment)	Likelihood of OCCURRENCE	Ability to DETECT the failure
9	Severe: Serious impact to QA of the output of the system/equipment and impact to final product quality attribute	Frequent: Failure is almost inevitable Consistent failures observed	Absolutely uncertain: Existing controls cannot detect the failure; no controls are in place
7	Major: Significant impact to QA of the output of the system/equipment and possible impact to final product quality attribute	Likely: Failure is likely and will occur in most circumstances. Repeated failures observed	Remote: Remote chance that controls will detect the failure. A control may be in place but is untested or unreliable
5	Moderate: Possible impact to QA of the output of the system/equipment and no impact to final product quality attribute	Occasional: Failure is probable at some time and has been observed	Moderate: A moderate chance that the control will detect the failure
3	Minor: Minor impact to QA of the output of the system/equipment and no impact to final product quality attribute	Unlikely: Failure could occur at some time. Only isolated incidents observed	High: Very likely that the control will detect the failure
1	Insignificant: No Impact to QA of the output of the system/equipment and no impact to final product quality attribute	Remote: Failure is extremely unlikely. No history of failure	Almost certain: The control will detect the failure in almost every

Table 7: Severity ratings.

		Severity Rating				
		1 Insignificant	3 Minor	5 Moderate	7 Major	9 Severe
Likelihood Rating	9 - Frequent	Medium	Medium	High	High	High
	7 - Likely	Low	Medium	High	High	High
	5 - Occasional	Low	Medium	Medium	High	High
	3 - Unlikely	Low	Low	Medium	Medium	High
	1 - Remote	Low	Low	Low	Low	Medium

Table 8: Detection ratings.

		Detection Rating				
		1 Almost certain	3 High	5 Moderate	7 Remote	9 Nil
Rating from Table 7	High	Low	Medium	High	High	High
	Medium	Low	Low	Medium	High	High
	Low	Low	Low	Low	Medium	Medium

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Derek Mullins is Senior Manager in Amgen's corporate engineering division with responsibility for clean and plant utilities across Amgen's network. He has over 20 years of experience in the biopharmaceutical sector, and has extensive experience in integrating sustainability within a regulated environment. He is a Chartered Mechanical Engineer, a Certified Energy Manager, and Lean Six Sigma Black Belt. Derek has been an ISPE member since 2004.

Keith Shuttleworth served as an Engineering Officer in the Merchant Navy where he was involved in both the theoretical and practical aspects of steam production, distribution, and usage in a number of applications such as propulsion, power generation turbines, pumps, heating, and distillation. He worked as an Engineering Manager in the UK's National Health Service and the pharmaceutical industry, where he has been responsible for both plant and clean steam generation/distribution. For the past 27 years, Keith has worked as a consultant providing advice and training on steam sterilization and steam quality, while developing and selling equipment for the testing of steam quality. He has been a member of two PDA Task Forces for the generation of PDA Technical Report Nos. 1 and 61 and has presented at PDA and ISPE venues on a number of topics. Keith worked as a Registered Authorising Engineer (Decontamination) from 1994 to 2019.

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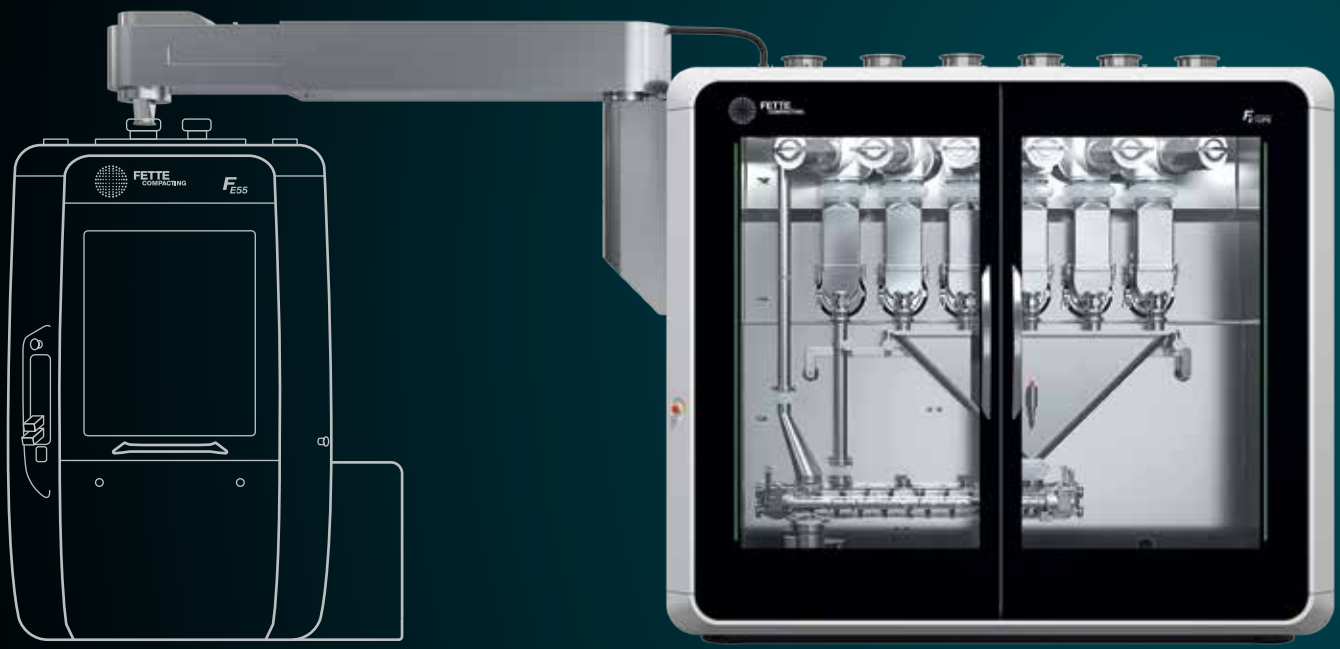

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