PHARMACEUTICAL ENGINEERING®

The Official Magazine of ISPE

January/February 2024 | Volume 44, Number 1

GAMP®

Machine Learning Risk and Control Framework

Quality Considerations in Disaster Recovery: A Case Study

The Use of Infrastructure as Code in Regulated Companies

ISPE®

ISPE.org/pharmaceutical-engineering

Delivering Solutions to Better Serve Your Patients

ENGINEERING

PROCUREMENT

CONSTRUCTION

CQV SERVICES

SINGLE POINT ACCOUNTABLE

Leverage our subject matter experts to accelerate your product delivery platform schedules with quality solutions.

BIOTECHNOLOGY | PHARMACEUTICAL | VACCINES

For decades, Fluor has designed and built various types of biotech and bulk pharmaceutical facilities, employing batch, semi-continuous, and continuous operations. We offer the life sciences industry agility and robustness through expertise in process design while providing innovative professional and technical solutions.

www.fluor.com

FLUOR®

PHARMACEUTICAL TRAYS USED BY THE TOP PHARMA COMPANIES

Pharmaceutical processing & handling solutions that are easily integrated with automated machinery.

Vial Trays
Model No. 229108

VIAL TRAYS

» Tapered front lip for easy loading
» Smooth, non-porous surface is easy to clean
» Vial gates available for various temp ranges

Gel Cap Drying Trays
Model No. 642008
with Heavy-duty
Aluminum Universal Dolly

GEL CAP DRYING TRAYS

» Ventilated sides or ends for quicker drying
» Interlock stacking without warping or distortion
» Won't bend, dent or deflect under heavy loads
» Smooth surface is easily cleaned
» Easy integration with process equipment

Deep Storage Stacking Box with Lid
Model No. 808208 and 808218 (Lid)

DEEP STORAGE TRAYS

» Ideal for storing gel caps prior to packaging
» Stacking design ensures product protection and saves valuable work and storage areas
» Smooth surface is resistant to mild acids and alkaline solutions

Slotted
Container with Lid
Model No. 808308

STERILIZATION & BIOTECH TRAYS

» Great for handling, storing and shipping small parts
» Slotted and unslotted containers available
» Ideal for Gamma, Autoclave and ETO environments
» Optional lids and dollies available

Reinforced composites bring a new level of performance to pharmaceutical processing and handling. **The leading name in FRP is MFG.**

NSF Made in the USA

MOLDED FIBER GLASS TRAY COMPANY
PH 800 458.6050 • www.mfgtray.com

MFG TRAY

PHARMACEUTICAL ENGINEERING®

JANUARY/FEBRUARY 2024

ON THE COVER Evolving approaches and expanded use of software tools and automation are represented on this cover.

Collaborate with us; we'll do the rest.

Simplify your project delivery with one point-of-contact managing a diverse supply chain and providing technical expertise for your collaborative, single-source solution.

IPS provides Engineering, Procurement, Construction Management, and Validation (EPCMV) services with one team. We have the expertise, community of partners, and transparency you need for the rapid delivery of complex projects with tight deadlines and costs from start to finish on your life sciences capital projects.

Knowledge, Skill & Passion

www.ipsdb.com

ips

36 LEVERAGING *GAMP® 5 SECOND EDITION* FOR MEDICAL DEVICES

This article provides a brief introduction into the standards and regulations for medical devices. It compares the *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* and applicable ISPE GAMP Good Practice Guides against the relevant regulations and standards for the development of software for medical devices and demonstrates *GAMP® 5 Second Edition's* applicability.

DEPARTMENTS

PEOPLE + EVENTS

TECHNICAL

ISPE

PHARMACEUTICAL ENGINEERING

Volume 44, Number 1

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

Editor-in-Chief: Nina Wang

Technical Copy Editor: Heather E. Saunders

Publications Coordinator: Marcy Sanford

Advertising and Sales
Laneisha Walker, Sales Operations Manager
lwalker@ispe.org

Carol Nettles, Advertising Sales Manager
+1 404-347-1755 cnettles@ispe.org

JT Hroncich, Advertising Sales Manager
+1 404-347-4170 jhroncich@ispe.org

Stock Photography and Illustration
iStock

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

Printing
Sheridan NH

Letters to the Editor
Letters must include the writer's full name, address, and organization. Letters may be edited for length and clarity. Send correspondence to PEmag@ispe.org

Limitation of Liability
In no event shall ISPE or any of its affiliates, or the officers, directors, employees, members, or agents of each of them, or the authors, be liable for any damages of any kind, including without limitation any special, incidental, indirect, or consequential damages, whether or not advised of the possibility of such damages, and on any theory of liability whatsoever, arising out of or in connection with the use of this information.

Article reprints can be ordered through Sheridan Content Solutions at sheridancontentsolutions@sheridan.com

ISPE Headquarters
6110 Executive Blvd., Suite 600
North Bethesda, MD 20852 US
Tel: +1 301-364-9201

ISPE Operations
3001 North Rocky Point Drive East
Suite 200-242
Tampa, Florida 33607
Tel: +1 813-960-2105

US Postmaster
Send change of address to:
Pharmaceutical Engineering Magazine
3001 North Rocky Point Drive East
Suite 200-242
Tampa, Florida 33607 US

Periodicals postage paid at Tampa, Florida, US, and additional post offices

Canada Postmaster
Send change of address and undeliverable copies to:
Pharmaceutical Engineering Magazine
PO Box 122
Niagara Falls, ON L2E 6S8
Canada

Canada Post mail agreement #40012899

Validate your MTP files **FOR FREE!**

Plug & Produce in Life Sciences with MTP

zenon MTP Suite for Equipment Producers (PEA) and End Users (POL):

- *Increase flexibility and reduce engineering and validation effort due to modular process automation*
- *Create or edit Module Type Package (MTP) files*
- *Validate your MTP files according to VDI/VDE/NAMUR 2658*
- *Manage your MTP library based on a central repository incl. versioning*
- *GMP-compliant HMI package for Process Equipment Assembly (PEA)*
- *Simplify the process orchestration of your equipment with a graphical editor (zenon POL)*
- *Integrate your existing skids using an MTP Gateway (independent from hardware and OS)*

go.copadata.com/mtp

Gold Microsoft Partner

GAMP 5

FDA 21 CFR Part 11 Compliant

zenon by COPA-DATA

By Scott W. Billman


Scott W. Billman

Opportunities for Growth and Expansion

Next year promises to be a busy one for ISPE. The year starts with the 2024 ISPE Facilities of the Future Conference in San Francisco and is quickly followed by the 2024 Aseptic Conference in Vienna. Both conferences bring together key technical talent from across the industry to engage in critical discussions about the future of delivering safe and effective products to patients around the world.

ISPE CONFERENCES AND COMMUNITY COLLABORATION

A common theme across the ISPE conferences is the digitization of everything we do. From basic GMP automation and systems to artificial intelligence use in the industry, our conference attendees are presenting on and discussing how we will continue to automate and digitize our work.

This issue of *Pharmaceutical Engineering*® magazine includes many articles about GAMP® and its importance to this digital transformation journey. In 2022, the FDA issued their draft guidance "Computer Software Assurance for Production and Quality System Software." Our GAMP community continues to stay current on these topics to ensure we have the most up-to-date and relevant information to discuss and collaborate on.

More than 30 years ago, a group of dedicated and passionate volunteers developed a special interest group to bring together the various thoughts and efforts around computerized system compliance. Through the years, this group has grown in size and popularity. As one of the leading ISPE Communities of Practice (CoPs), the GAMP CoP drives industry-wide standards and practices that are referenced globally with the GAMP Guides.

Opportunities to become involved with GAMP continue to grow around the world. In 2023, new local GAMP CoPs were created in New Jersey and Boston in the US, as well as GAMP South Asia, which includes Australia, Indonesia, Malaysia, Philippines, Singapore, Thailand, and New Zealand collectively. These local CoPs each need new volunteers to lead them and to create events that are tailored to their location and members' interests. If you are interested in volunteering, please reach out to one of the local or international CoPs for more information.

Volunteer Engagement and CoP Growth

Volunteer engagement and the growth of CoPs is a key element of the 2023–2025 ISPE Strategic Plan. ISPE was founded on, and grew through, volunteer engagement and activities. I personally engaged in various local ISPE Chapter events, committee positions, and local Chapter leadership for many years. Local Chapters and Affiliates provide you with easily accessible events and programs, along with the opportunity to network and engage with local and regional industry stakeholders. Many CoPs have local, regional, or international groups as well.

Your design and build partners

— bringing your life sciences project to life.

Our services

A proven approach within the highly regulated life science sector

- Strategy
- Design and engineering
- Project management
- Construction

LEARN MORE

Featured thought leadership

In an era of AI and digital progress, life sciences must evolve to stay ahead. Learn more about our concept, FutureLabs.

READ MORE

Spark Brilliance.

There are more than 20 active CoPs with enthusiastic volunteers and contributors around the world that engage in relevant topics, guide development, and create conference material. Reach out to any staff member or ISPE leader to see how you can get more involved today.

Global Expansion

Another key strategic pillar is global expansion to reach areas previously underserved by ISPE. International leadership continues to support geographic expansion to areas such as South America, China, and Southeast Asia. One example of that expanded reach of ISPE technical knowledge is a program that was coordinated through the ISPE Foundation and made possible by a generous corporate donation. An ISPE guidance document and training course materials in biotechnology manufacturing topics were translated to Portuguese for use in Brazil. This was done in collaboration with the ISPE Brazil Affiliate, the Brazilian Academy of Pharmaceutical Sciences, the University of São Paulo, and Agência Nacional de Vigilância Sanitária, Brazil's National Health Regulatory Agency.

The training was rolled out to approximately 130 participants comprised mainly of regulatory authorities, industry members, students, and emerging leaders. The paired guidance document, the *ISPE Guide: Advanced Therapy Medicinal Products (ATMPs)—Autologous Cell Therapy*, will soon be available to local targeted audiences. Throughout 2024, the International Board of Directors and ISPE leadership will continue to look for impactful areas to further engage and bring the vast technical advice and knowledge, developed by our dedicated volunteers, to more areas of the globe.

MOVING FORWARD AS ONE ISPE

I want to take this opportunity to thank all the dedicated volunteers who have taken on leadership roles across the various efforts and regions. This includes Chapter and Affiliate leaders, the International Board of Directors, the ISPE Foundation Board of Directors, CoP leaders, conference planning teams, guide and document writers and reviewers, and our various regulatory committees.

It is only when we work together, as One ISPE, that we can continue to bring high-quality, technical, and relevant topics to our membership across the globe. It is through the continued collaboration and partnerships we have developed that we will continue to share this knowledge globally to ensure we are bringing cutting-edge technology and solutions into the industry and driving toward life-saving therapies available globally to patients.

Scott W. Billman is Vice President of Engineering for Pharmaceutical Services at Thermo Fisher Scientific and the 2023–2024 ISPE International Board Chair. He has been an ISPE member since 1996.

We understand how leading-edge products and process improvements are critical in your business.

INNOVATE + ACCELERATE

You are enabled to achieve a faster time to market, improve plant productivity and reduce risk.

Endress+Hauser helps you to improve your processes:

- With the largest range of innovative and compliant measuring instruments, integrated calibration solutions and the latest instrument diagnostics
- With standardized project engineering and project management as well as a service portfolio that focuses on higher productivity

Do you want to learn more?
www.endress.com/life-sciences

Endress+Hauser
People for Process Automation

By Vivien E. Santillan


Vivien E. Santillan

THE FUTURE OF WOMEN IN PHARMA®

An ISPE campaign in 2016 piqued my interest in the Women in Pharma committee because I'm an advocate for women in the workplace. When I became President of the ISPE Philippines Affiliate in 2017, I knew that Women in Pharma should be included in the affiliate's program. The committee provided a platform for conversations on professional and personal development for members' career advancement. And personally, this started my journey with Women in Pharma.

WOMEN IN PHARMA GROWTH

Women in Pharma has grown globally through its member initiatives in the Affiliates and Chapters. The journey was not easy, as we needed to introduce the mission and vision of the committee to the ISPE community. Several projects and initiatives began during the pandemic when we had limited connections. Women in Pharma provided the tools necessary for collaboration and meaningful conversations through webinars, where members could network regardless of their location and time zone.

Since its inception, the Women in Pharma International Steering Committee has provided the needed direction for the committee that has served as its guiding principle to succeed. As I assume the role of Chair for the Women in Pharma International Steering Committee, I'll encourage us to continue to maximize the impact women can make in our industry and respective communities and advocate for the committee to serve as an environment for positivity and inspiration. Programs with a focus on personal and professional growth with social impact at their core will shape the future of the pharmaceutical industry. Building and nurturing allyship with our colleagues in the industry will progress with the aim of advancing inclusion.

The Mentor ISPE Program that started in 2023 and received an outstanding response from students, Emerging Leaders, mid-level managers, and executives will continue into 2024. It is a testament to how greatly our community desires to connect with fellow members as mentors and mentees. Through this program, where diversity of thought thrives, members can relate to like-minded people. It provides a platform for learning different perspectives on varied topics through conversations that may inspire growth.

Programs with a focus on personal and professional growth with social impact at their core will shape the future of the pharmaceutical industry.

A YEAR OF TRANSFORMATION AHEAD

Next year is a leap year, and some people believe that is associated with disruption and transformation. It is also the Year of the Dragon, which is believed to be a year of luck and prosperity. In the pharmaceutical industry, innovation and development will continue, with personalized medicines, artificial intelligence-driven drug development, demand for biologics, and advanced therapy.

Let us all welcome 2024 with positivity and continue our journey toward how we can do better and provide opportunities to grow. Stay updated and participate in Women in Pharma activities in your Affiliate or Chapter and at ISPE's global conferences. Women in Pharma will continue to connect, collaborate, and inspire.

Vivien E. Santillan is Regional Director for Asia at Novatek International and the 2023–2024 Chair of the Women in Pharma International Steering Committee. She has been a member of ISPE since 2012.

By Monique L. Sprueill


Monique L. Sprueill

WHAT IS GAMP® AND WHY IS IT IMPORTANT?

ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition) outlines how to apply a risk-based approach to GxP computerized systems and is aligned with the FDA draft guidance "Computer Software Assurance for Production and Quality System Software."

These practices ensure that computerized systems, which support manufacturing and other GxP operations, adhere to regulatory requirements, maintain data integrity, and consistently yield products that meet industry standards.

CRITICAL THINKING FOR COMPUTERIZED SYSTEMS

As Emerging Leaders (ELs), we should prioritize developing critical thinking. It is used to assess risk, determine the level of interaction with internal and external stakeholders, and ensure that the appropriate controls are established. *GAMP® 5 Second Edition* is an essential tool to help us prove that the systems we design, build, and deploy effectively operate as intended.

ISPE GAMP® 5 Second Edition focuses on the quality aspects in the application of agile frameworks, cloud computing, blockchain, artificial intelligence, and machine learning. It highlights the importance of critical thinking when executing quality risk management and throughout the system life cycle. According to the guide, "proactive adoption of a risk-based approach suitable for the intended use of the computerized system takes into account the multiple layers of assurance provided elsewhere within the business process" [1]. It enables better project planning and execution.

Pharmaceutical research, development, and commercial operations rely on computerized systems for product quality, consistent yields, and business continuity. Drug approvals require successful clinical trials. How information is collected, managed, maintained, and distributed provides confidence in the reliability of trial data. Technical and functional specifications determine equipment capability requirements. During the entire life cycle of a drug, we use analytics to convey a state of control, equipment capabilities, and process performance information to management and stakeholders.

How to Apply GAMP Guides

ISPE GAMP Guides and Good Practice Guides cover the system life cycle, infrastructure, testing, operations, and innovation. They provide baseline information to help increase knowledge of computerized system compliance and computer software assurance and they demonstrate how to apply the principles.

The GAMP Global Steering Committee and the regional and local GAMP Communities of Practice (COPs) provide a platform for continuous learning and innovation. Actively participating in COPs is a great way to expand your network, increase your capabilities, and develop relationships with industry professionals. The ISPE Engage Open Forum is a space where you can ask questions with no fear of judgement, discuss ideas, and share lessons learned. You can also partner with others in your network to present at a conference, write a blog, or submit an article for inclusion in *Pharmaceutical Engineering®* magazine.

What Are the Next Steps?

If you are not a member of ISPE, join today (www.ispe.org). Actively participate in EL activities in your local Affiliate or Chapter. Access GAMP resources and connect with the GAMP Global Steering Committee. You can join a local GAMP CoP. Or, if there's not one in your area, align with your local Affiliate or Chapter and start one. Add GAMP content, questions, and ideas to the ISPE Forum. Write a blog or article. Talk with your manager and colleagues about presenting your project at a conference or local program.

CONCLUSION

One of the first lessons I learned when I joined ISPE is that my network is one of the most valuable assets to acquire. People in your network will help you gain a better understanding of GAMP and how to apply the principles to ensure data integrity and regulatory compliance and that GxP-regulated information systems are properly maintained.

Reference

1. International Society for Pharmaceutical Engineering. *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)*. North Bethesda, MD: International Society for Pharmaceutical Engineering, 2022.

Monique L. Sprueill, CQA, CMQ/OE, PMP, is Director, GCP Quality Lead at Bristol Myers Squibb and the 2023–2024 International Emerging Leaders Chair. She joined ISPE in 2002.

MACHINE LEARNING RISK and Control Framework

By Rolf Blumenthal, Nico Erdmann, PhD, Martin Heitmann, Anna-Liisa Lemettinen, and Brandi Stockton

Stakeholders across industries are becoming accustomed to using information technology (IT) systems, applications, and business solutions that feature artificial intelligence (AI) and machine learning (ML). Even though some of these uses show phenomenal performance, thorough risk management is required to ensure quality and regulatory compliance are met within the life sciences industry. By leveraging specialized frameworks and methods, we compiled a holistic framework to dynamically identify, assess, and mitigate risks when AI and ML features are in use.

A RISK-BASED APPROACH TO AI AND ML

After years in which AI initiatives commonly failed to pass the pilot stage, the operational use of AI applications within the life sciences industry is evolving and rapidly gaining momentum. With a substantial increase in regulatory approvals and AI applications like ChatGPT being commoditized and granted higher levels of autonomy, it is imperative for the life sciences industry to implement a framework to review the risks of and controls for AI to maintain product quality, patient safety, and data integrity.

This article adopts the ICH Q9(R1) risk management process as a basis to address the specific challenges for AI systems. Along this harmonized risk management process, our framework—the ML risk and control framework—builds on recently developed AI methods and concepts to identify and assess the entire risk inventory for a given use case along the life cycle, represented in a risk analysis and mitigation matrix. The resulting framework offers a straightforward structure to continuously manage the complexity of ML-related risks throughout the system life cycle, from concept to operation. Furthermore, due to its ease of use, science-based approach, and transparency, the true value of the ML risk and control framework unfolds during periodic risk review by facilitating understanding and informed decision-making.

RAPIDLY EVOLVING AI AND THE NECESSARY RISK MANAGEMENT

The field of AI has rapidly evolved. The remarkable and swift transformation has marked an extraordinary pace of progress, driving disruption and fostering a wave of innovation across industries. According to the Stanford Institute for Human-Centered Artificial Intelligence's annual AI Index Report for 2023, the total number of AI publications has more than doubled since 2010, growing from 200,000 in 2010 to almost 500,000 in 2021 [1]. The use of AI within the life sciences has gained traction and is accelerating. According to the FDA, the number of approved AI-/ML-enabled medical device approvals increased by a staggering 1,800% since 2015, growing from 29 in 2015 to 521 as of October 2022 [2].

With the introduction of ChatGPT and other generative AI applications raising public awareness of its power, AI's potential use cases have also exponentially grown, which brings associated risks [3]. Such awareness sparked a surge in desire to exploit the potential of data and data-driven insights backed by numerous pilots and first productive applications.

The urge to integrate AI- and ML-featured technology into the production software system landscape is mirrored by several regulatory initiatives, including FDA discussion papers and European Medicines Agency (EMA) papers: *Artificial Intelligence in Drug Manufacturing* [4] and *Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products* [5] from the FDA, and "The Use of Artificial Intelligence (AI) in the Medicinal Product Lifecycle" [6] and "Concept Paper on the

Revision of Annex 11 of the Guidelines on Good Manufacturing Practice for Medicinal Products – Computerised Systems" [7] from the EMA.

However, both current and future initiatives will take time to develop because neither AI nor ML are mentioned in current GMP guidelines and regulations. This is unlike other areas like Medical Devices where some consensus on good ML practices has been established [8]. Conversely, multiple industry guidance documents exist, including the *ISPE GAMP® RDI Good Practice Guide: Data Integrity by Design* [9] and the *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* [10], elaborating on the principles for management of AI and ML components and subsystems throughout the life cycle from a high-level perspective.

Although risk management and criticality of operational monitoring are put into focus in these guidance documents, we identified a gap in its practical application. How can an organization manage risks and controls during the concept, project, and operational life cycle phases when there are so many choices in autonomy and control AI- and ML-featured IT systems, applications, and business solutions? As such, we compiled a holistic framework to operationalize the increased risk awareness of AI as exemplified by applications such as large language models or concepts like explainable AI [11]. Thus, from our point of view, it is important to establish an industry understanding on:

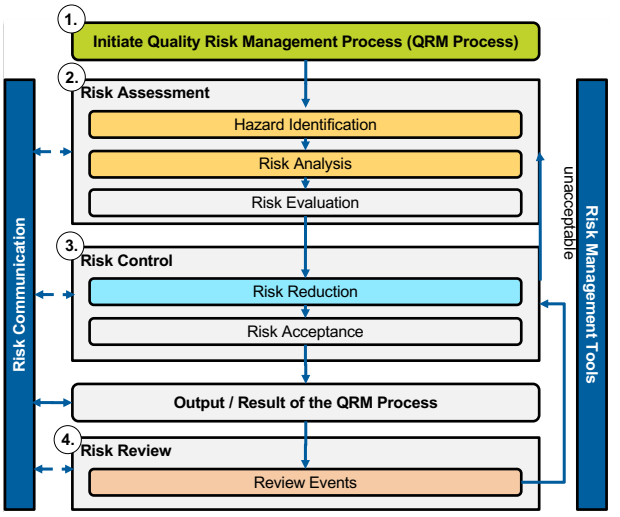
- The criticality of risks in various contexts of use during initiation of the quality risk management process
- A typical risk inventory along the life cycle of an ML subsystem and its integration into the computerized system landscape
- Suitable and appropriate risk mitigation strategies
- A dynamic process governing the life cycle, ensuring a continued state of control

FOUNDATIONS AND PRINCIPLES

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) published its first revision of the ICH Q9 guideline on quality risk management in early 2023 [12]. This guideline "offer[s] a systematic approach to quality risk management [and] serves as a foundation or resource document that is independent of, yet supports, other ICH quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment" [12]. As such, ICH Q9(R1) provides a high-level process, which is summarized in Figure 1.

The ICH Q9(R1) guidance is applicable to any process and system, agnostic of whether this system comprises ML subsystems. Therefore, from an operational risk management perspective, many questions remain unanswered when considering such components: the impacts and potential risks associated with data, the choice of models and training algorithms for risk management during productive operation, and the control of phenomena such as drift.

Figure 1: ML risk control framework embedded in the ICH Q9(R1) process diagram, with the focus areas of this article highlighted [16].



However, with ICH Q9 being the internationally harmonized guideline, we base our ML risk and control framework on key process steps to facilitate compliance with regulatory guidance and thus avoid additional complexity. We considered integrating the Second Draft of the ML Risk Management Framework published by NIST [13]; however, because guidance provided in this draft is less specific to the industry than ICH Q9(R1), we focused on the latter.

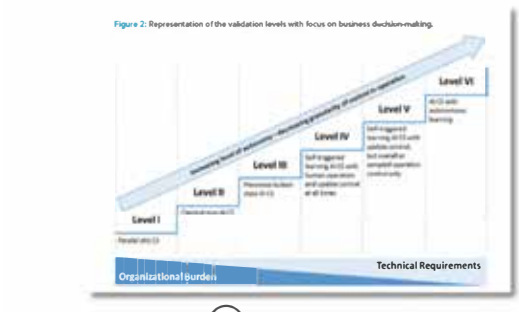
Because *GAMP 5® Second Edition* is widely adopted in the industry, we also base our framework on concepts provided in this guideline, particularly those in Appendix D11—Artificial Intelligence and Machine Learning [10]. Here, *GAMP 5® Second Edition* suggests a software development life cycle model for the development and computerized system integration of ML subsystems.

The GAMP Machine Learning Sub-System Life Cycle Model comprises three primary phases: concept, project, and operations. We use this model for navigating the risk landscape to facilitate a structured identification of hazards, considering organization-, data-, process-, and methodology-related facets in the area of ML methodology to build a comprehensive risk inventory.

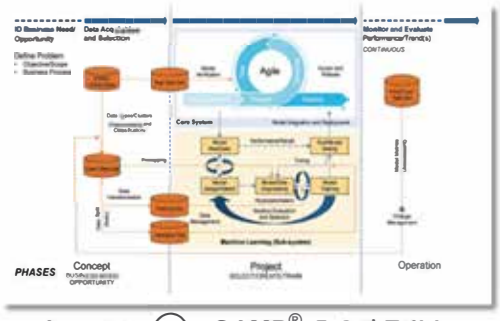
Further guidance has been developed, providing details of organizational aspects and blueprints for decision-making. Specifically, we extend the "AI Maturity Model for GxP Application: A Foundation for AI Validation" [14] and include concepts and ideas of the AI governance framework [15], particularly following the concept of AI quality dimensions.

We have adapted the risk analysis and mitigation matrix (RAMM) [16] as a template, using its representation of risks, risk assessment, and mitigation measures, and its concept of a dynamic, iterative interpretation of risks throughout the system life cycle.

Figure 2: Guidance and frameworks used to augment the ICH Q9 process by particularities for ML subsystems.



Input to (1.) : **AI Maturity Model**



Input to (2.) : **GAMP® 5 2nd Edition**

Input to (3.) & (4.) :
AI Governance & QA Framework

Input to (3.) & (4.) :
Risk Analysis and Mitigation Matrix (RAMM)

Based on these premises, this article proposes guidance that can be easily followed for the practical implementation of an appropriate ML risk and control framework. It is based on the following general principles, aligned with previously mentioned references and previous work:

- Commensurate effort: The risk and control framework yields solid reasoning on the risk strategy, respecting the organization's risk tolerance and the risk inherent in the process that is using ML methodology.
- Holistic view: The proposed framework helps identify risks that arise from development and operation of AI/ML models embedded in a computerized system. It integrates accepted data science methodology with the concepts of product quality and patient safety in the regulated areas of the pharmaceutical industry.
- Compatibility with accepted methodology: Risk management is not new—it has been practiced for decades, with a primary focus on classical, non-ML-enabled computerized systems. We aim for compatibility of widely adopted approaches, hence augmenting current approaches to risk control of GxP relevant processes with particularities of ML methodology.
- Dynamic process understanding: Further demonstrating that risk management is iterative, risk assessment will change as more process understanding is gained. This is particularly true for forward-looking methodology. Hence, the effectiveness and adequateness of risk mitigation measures should be assessed regularly to ensure the process is in human control and to unlock further opportunities in the scope and autonomy of the ML solution.

These concepts will be explored further in this article, providing generally applicable, though operational, guidance along key steps in the ICH Q9(R1) risk management process. Similar to the GAMP ML Sub-System Model, this framework is intended to be embedded into an existing risk management process for computerized systems to ensure additional ML-related risks are managed throughout the life cycle of the computerized system.

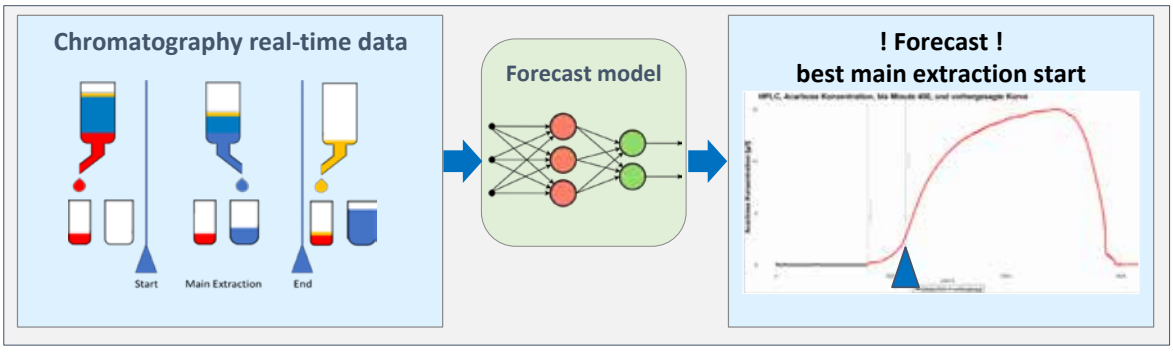
As with the overall ICH Q9(R1) risk management process, the framework is designed as a structured process to break down the ML-specific challenge of risk management. It is not meant as a one-time exercise and should accompany the model along its life cycle. The framework adds to the following segments to the ICH Q9(R1) process:

1. Initiate quality risk management process
2. Risk assessment (in particular, hazard identification and risk analysis)
3. Risk control (in particular, risk reduction)
4. Risk review

These additions are described in detail in the following sections and shown in Figure 2 [12]. The framework can further be used for extending the set of risk management tools to facilitate effective risk communication.

To illustrate its practical application, we accompany these concepts with the following example of downstream process optimization in biotech active pharmaceutical ingredients (APIs) through the quality control of a chromatography step. The

Figure 3: Exemplary downstream optimization use case.



objective of this ML application is to determine the optimal point to start and end the capture of the APIs, splitting undesired impurities from the downstream manufacturing (see Figure 3). The operator uses this information to execute the API capturing. The ML model is trained on historic data, balancing quality objectives on the API's purity and optimized yield of the resulting batch.

Initiate Quality Risk Management Process

In alignment with ICH Q9(R1), our risk management framework starts with the initiation of the quality risk management process. For ML applications, it is recommended to perform this during the initial planning phase by leveraging the AI Maturity Model [14]. The AI Maturity Model can be used to define expected autonomy as well as the control design level that together form the target operating model in the first productive ML-featured layout (minimal viable product, or MVP). Thereby, the autonomy describes the "feasibility to automatically perform updates and facilitate improvements." The control design is the "capability of the system to take over controls" [14].

The essence of the AI Maturity Model is the six maturity levels on which use cases can be classified. It also can be used to define the evolution of the ML-enabled computerized system and provides a first indication of the potential risk with regard to the selected ML application and use case design [14].

The AI Maturity Model can also be used to define the evolution of the ML-enabled computerized system and provides a first indication of the potential risk with regard to the selected ML application and use case design [14].

The maturity levels are as follows:

- Level I: System is used in parallel to the production process
- Level II: Non-AI applications
- Level III: Applications used in locked state
- Level IV: Autonomous with self-triggering learning—humans are in the loop, but they are used in combination with humans in operation who also control updates at all times
- Level V: Autonomous with self-triggering learning—without humans in the loop; human control relies solely on sampling after operations
- Level VI: Completely autonomous—optimizing either toward a defined goal or a direct feedback loop

Based on the AI Maturity Assessment, we move forward toward a holistic approach to identify potential GxP hazards as part of the ML risk and control framework. The maturity levels of the AI Maturity Model (i.e., clustering of autonomy and control design levels) should be mapped against the potential risk impact. The risk impact in terms of data integrity, product quality, and patient safety relates to the potential to impact the patient. The risk impact can be used to group applications:

- Indirect impact only
- Direct impact on GxP processes but no direct impact on patient safety
- Direct impact on patient safety via drug release
- Direct and immediate impact

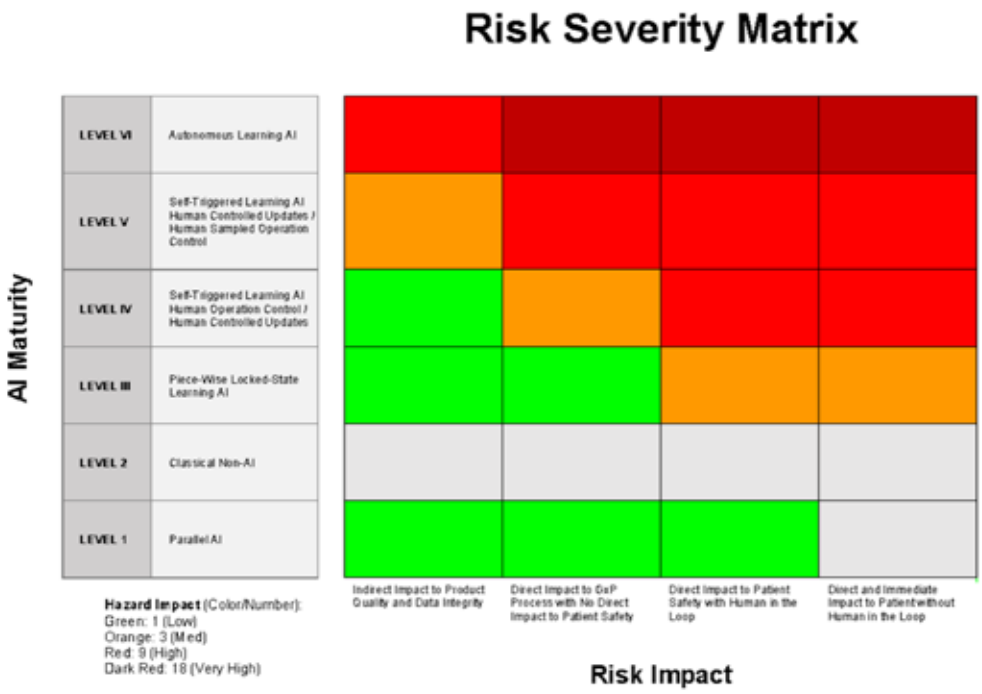
On the far-left side of the risk impact matrix (see Figure 4), we find applications with indirect impact on product quality and data integrity. Examples are AI applications supporting post-marketing surveillance analysis or prioritization of complaints.

The second group comprises applications with direct impact on GxP processes, product quality of starting materials, or intermediate products, but no direct impact on patient safety. Examples are applications defining the right time for harvesting during the upstream process of cell growth. The chromatography example previously described would fall into this category.

The next group is made of applications involved in the production of the final pharmaceutical product, or the control and final approval by the drug release instance—for instance, the qualified person in the European Union and the quality department in the US. Applications in the last group, such as software-as-a-medical-device or software-in-a-medical-device, have a direct and immediate impact on patient safety. Based on the AI maturity level and the risk impact, the hazard impact can be defined.

The hazard impact—depicted in Figure 4 in green (low), orange (medium), red (high), and dark red (very high)—is the first level of risk assessment of an AI application in this risk and control

Figure 4: Risk severity matrix defining the hazard impact based on the AI maturity level and the risk impact.



framework. It should be noted that gray in the picture does not mean that no risk is associated, but that the risk is not ML specific. As illustrated in the following sections, the hazard impact is a central lever to be reviewed during the implementation. It will help determine whether the overall risk is acceptable for the AI system and to fine-tune it according to the risk appetite of the company, as illustrated in later sections.

In terms of the chromatography example, the hazard impact is determined to be low. The application is categorized as level III on AI maturity because the application is used in a locked state: the model is only trained once and only retrained and revalidated on an individual basis. Furthermore, from a control design perspective, the application switches the fractions that can immediately be revoked by the applicant. From a risk impact perspective, the example has a direct impact on the GxP process and product quality but no direct impact on patient safety because a multitude of quality control measures follow.

Risk Assessment

Key to the risk control process is a holistic view on risks potentially affecting product quality or patient safety. Only if risks are identified can adequate risk control measures and monitoring procedures be defined—a "blind spot" might have an immediate impact on the quality objectives. However, ML-enabled applications are typically used in an environment of complexity. Often, a primary reason to opt for such a solution is to draw insights from complex input data and leverage complex algorithms consisting of various model layers and large parameter sets.

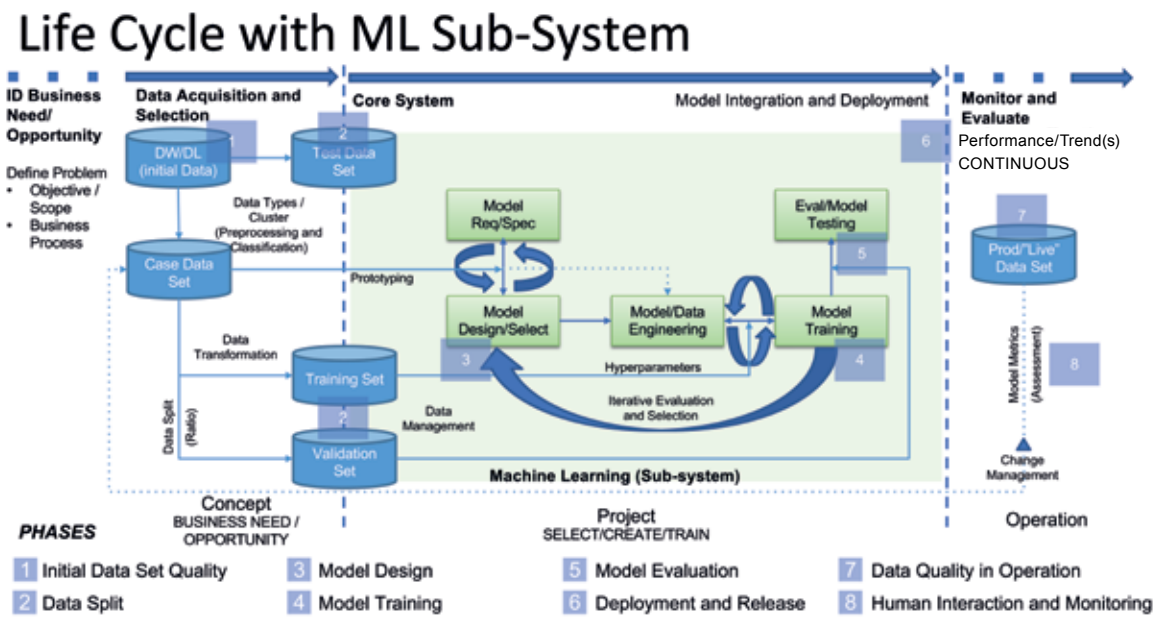
In addition, quality measures are statistical figures, which introduce an additional layer of uncertainty from a risk control perspective. Therefore, we deem a structured approach to the risk identification necessary, leveraging process understanding of how ML-enabled solutions are constructed and critical thinking reflecting on the specific use case.

GAMP 5® Second Edition [10] introduced a life cycle model for the development of a ML subsystem in its Appendix D11. This life cycle consists of three major phases:

1. Concept phase: The intended use is described by means of business, functional, and processual considerations. In addition, the availability and quality of data for training and productive operation are assessed.
2. Project phase: Uses an iterative approach for data, models, and their hyperparameters, as well as model evaluation, to then shift toward a verification, acceptance, and release step. The iterative nature of this process reflects a growing understanding for data, processes, and the intended use. Subsequently, the verification and acceptance steps are designed to provide evidence as to whether quality objectives are met to prepare for a robust release.
3. Operation phase: The ML subsystem is integrated within the computerized system architecture and serves its intended use, often in combination with human operators ("human-AI team"). During this phase, continuous monitoring must be performed and may result in changes or modifications to the AI/ML subsystem.

Following this life cycle model, we identified eight hazard clusters that should be assessed from a risk control perspective to prepare

Figure 5: Hazard clusters identified in the life cycle model.



for the next stage of defining risk control and mitigations measures (see Figure 5).

In the following, the hazard clusters are elaborated including their rationale and their relevance in the context of product quality and patient safety in a GxP environment. The rationale follows the observation that, due to the statistical training and evaluation mechanics, every data point carries importance for the overall model. For this reason, inaccuracies in early stages, such as the data set identification or during model selection, may propagate to the production environment, as the evaluation in the test stage includes statistical uncertainty on its own. The rationales are thereby supported by the following risk inventory examples.

1. Initial data set quality

The quality of the case data set is crucial for the expected performance in operations. This data set must be able to provide enough representative data to a) train models on the actual intended use and b) ascertain the model performance in the test stage. If the initial data quality is low, the iterative learning process may be compromised.

Examples:

- The chosen data set is not adequately representative for the real-world application (selection bias).
- Labels of data may be inaccurate, which yields inferior directions to the training procedures and evaluation via key performance indicators during testing.
- Inaccuracies in data transformation applications ("Extract-Transform-Load") lead to a wrong case set for learning and testing.
- Data augmentation techniques to complement base data are implemented inaccurately, posing a risk to representativeness.
- Data augmentation techniques may be more customized to the data used for the model development (training, validation, and test stages), which could lead to inferior performance during operations.
- Insufficient or inaccurate harmonization of data may blur the training, validation, and evaluation process, which may yield an inferior model performance.

2. Data split

Data splitting is a crucial task for being able to adequately test the performance before production on a data set not yet used for model development. If the data split yields a test data set that is not representative for productive use, a performance drop may occur in the operations phase.

Example:

- During determination of the training, validation, and test data sets, the test data set is not adequately representative anymore, which may distort key performance indicators and the final acceptance decision; if positive, immediate risk for product quality emerges.

3. Model design

An inferior model design (e.g., with a suboptimal choice of the modeling approach) may yield a less accurate model; in conjunction with progressive quality objectives, this causes a necessary higher risk to product quality or patient safety.

During operations, it must be ensured that the human is in control, otherwise an immediate risk regarding product quality, and eventually patient safety, arises.

Examples:
- Inferior choice of model yields suboptimal performance given data and use case.
- The intended use may not closely match the actual real-world application, causing downstream risks to later steps in the project and operation phase.
- Quality expectations are too optimistic, posing higher risks to product quality and patient safety.

4. Model training

On a similar note, as for the model design, but on a more detailed level, the search for an optimal set of features or hyperparameters may be stopped too early, causing a higher risk to product quality or patient safety.

Examples:
- Inferior selection of data (feature engineering) yields suboptimal performance regarding the quality objective profile.
- Iterative fine-tuning is stopped too early, which yields a suboptimal performance in the actual process, and hence risk to product quality and patient safety.
- The algorithm itself carries inaccuracies, while mistakes are overlooked because of the model complexity, which adds the risk of unexpected behavior in the production phase.
- The modeling path, design decisions, and fine-tuning process are not adequately documented, which yields user and inspector acceptance risks (resulting in a non-GxP risk, but a regulatory risk).

5. Model evaluation

The model evaluation is the final acceptance test before production; bias in the evaluation may yield an acceptance decision that does not conform to the organization's established risk appetite.

Examples:
- The test data is more benevolent to the model than in median cases—which may yield low performance in operations, and hence a wrong acceptance choice and immediate risk to product quality.
- Inaccuracies in the model integration (i.e., provisioning of data, extracting model results) distort model performance, posing the risk of a wrong acceptance decision.
- Evaluation routines include inaccuracies, posing a risk to life cycle decision-making.

6. Deployment and release

Throughout the training and fine-tuning process, a large set of models is estimated. The wrong model choice for deployment and release poses an immediate risk to product quality and patient safety in the operations phase.

Examples:
- Out of a selection of possible iterations in the development process, the wrong model is deployed, which yields a nonvalidated and a possibly inferior or inadequate model in production.
- The infrastructure may not be adequate to support productive use, given the complexity of the ML model and possible explainability add-ons. This in turn may cause delays in decision-making along the productive process, and hence a risk to product quality.

7. Data quality in operation

If data quality does not meet the expectations as per evidence generated by use of the test data set, a loss in performance must be expected. Depending on the chosen operating model, and the degree of autonomy, a direct impact due to the decisions of the ML-enabled application, or at least an indirect impact due to confusion of operators, is expected.

Examples:
- The distribution of real-world data may gradually shift as, for example, in areas with lower statistical performance. This may yield more false positive cases or larger errors, as specified in the quality objectives.
- External or internal data sources may change syntax or semantics during runtime, which might not be reflected in the model, and cause a drop in performance and a risk to product quality depending on the use case.
- When relying on data or models provided by third parties, this may not be available according to the service level agreements, which may introduce a risk to the model performance and, therefore, product quality.

8. Human interaction and monitoring

During operations, it must be ensured that the human is in control, otherwise an immediate risk regarding product quality, and eventually patient safety, arises. The effectiveness of risk mitigation measures and performance of the human-AI team crucially depends on the design of monitoring and human interfaces.

Table 1: Examples of hazards from the downstream process optimization use case.

Hazard Cluster	Hazard	Implication	Rationale and Comments
Initial Data Quality	Insufficient data was provided for training and testing.	The trained model might lack generalization; this might not be identified in the test step due to ranges of the data input space not sufficiently covered.	If the necessary data has not yet been collected, it is best to first accumulate sufficient data to estimate a more robust model. The sufficiency of the data can only be determined by experiments and by means of process and subject matter understanding.
Data Quality in Operation	Granularity of input time series data for productive use is less than expected.	If fewer data points are provided in the time series than expected, the accuracy of the prediction is insufficient, translating to a use of the model in a nonvalidated input space area.	This hazard is quite typical when comparing training and test data. Much effort may have been invested into assembling suitable input data, while input data quality considerations might not be feasible in the productive context. Therefore, the nature and expectations regarding input data have to be clearly defined and validated in the acceptance step.
Data Quality in Operation	Real-world data covers areas in the input space that have not been represented in the training and test data set.	If the characteristics of some time series are not reflected in the training and test data set and with inadequate generalization of the model, the accuracy of the prediction may be insufficient, in turn giving rise to product quality risks.	Whether this hazard indeed leads to product quality implications depends on various characteristics of the model and the input data, e.g., the model's generalization capabilities or the number of violations and the distance of the input to statistical mass in the training and test data set.

Examples:

- Features to facilitate human-machine interaction may be insufficient even after acceptance in the evaluation stage, which yields inferior decision-making or loss of time, and hence introduces a risk to product quality.
- Limitations and control of the ML-enabled system may be insufficient, so that decisions are based on uncertain outcomes.
- The monitoring may include inaccuracies or blind spots, posing a risk model for life cycle decisions (e.g., retraining or model redesign), which may yield undesired drift and gradual loss of model accuracy.
- For online learning systems, model drifts can pose a risk to the performance and reliability of the model, hence a lack of control in the production process.

As an excerpt for the chromatography optimization use case, Table 1 shows selected examples of risks according to their hazard cluster.

All identified hazards must be analyzed and evaluated. There are several classic risk management methods from fishbone diagrams to failure mode and effects analysis (FMEA). For IT systems, FMEA or variations of FMEA, which do not rely on risk priority numbers, are commonly used across the industry.

When it comes to complex processes and processes with continuous expected improvement, classical methods like FMEA are getting to their limitations. With increased complexity, the documentation for FMEAs expands, which results in the loss of transparency. This is particularly true if risks from different processes need to be put into perspective. As for complex processes, it is likely that some parts have inherently higher impact than others. An example of this is the drug manufacturing process, in which certain steps (e.g., preparation steps) have an intrinsically higher impact on data integrity, product quality, and patient safety than others.

For the specific example of drug development evaluation, the RAMM model was developed. The original RAMM model combines the risk rating of process steps with the individual risks. Via color coding, the visualization of risks across process steps for diverse critical quality attributes (CQAs) is achieved, which is not possible with other models.

As part of the RAMM model, the CQAs are listed on the Y-axes. For each CQA, the relative importance is determined, which reflects the relative impact of the CQA on product quality and patient safety. On the X-axes, the process steps and the process parameter, or the respective process attribute, are listed.

For controlling the risk of AI applications in more detail, we propose an adapted version of the RAMM model that reflects the complexity of the ML development cycles and facilitates the risk review, which is particularly critical for continuously improving systems. It thereby leverages the hazard impact level of the risk initiation as a hazard impact factor (HIF) and the hazard clusters of the hazard identification. In addition, it uses the quality dimensions of the AI Governance and QA Framework, as outlined in "AI Governance and Quality Assurance Framework: Process Design," [15] for the risk evaluation.

Figure 6: Sample of the AI RAMM sheet for the given use case.

Hazard Impact Factor		9												
Quality Dimension			Data Quality Mgmt.		Human-AI Interaction		Predictive Power		Stability		Calibration			
Hazard Clusters	Hazard Cluster Total Score	Risks	RA	RA * HIF	RA	RA * HIF	RA	RA * HIF	RA	RA * HIF	RA	RA * HIF	Total Score	Risk Control Measure
Initial Data Set Quality	198	Risk 1	Low	9	Low	9	Low	9	Low	9	High	81	117	
		Risk 2	Low	9	Low	9	Low	9	Medium	27	Medium	27	81	
Data Split	261	Risk 1	High	81	Low	9	Low	9	Low	9	Low	9	117	
		Risk 2	Medium	27	Low	9	Low	9	Low	9	Low	9	63	
		Risk 3	Low	9	Low	9	Medium	27	Low	9	Medium	27	81	
Model Design	135	Risk 1	Medium	27	Medium	27	Medium	27	Medium	27	Medium	27	135	
Model Training	153	Risk 1	High	81	Medium	27	Medium	27	Low	9	Low	9	153	
Model Evaluation	117	Risk 1	Low	9	Low	9	High	81	Low	9	Low	9	117	
Deployment and Release	81	Risk 1	Medium	27	Low	9	Low	9	Low	9	Medium	27	81	
Data Quality in Operation	63	Risk 1	Low	9	Medium	27	Low	9	Low	9	Low	9	63	
Human Interaction and Monitoring	135	Risk 1	Medium	27	High	81	Low	9	Low	9	Low	9	135	

RA = Input Risk Assessment, RA*HIF = Risk Assessment weighted by Hazard Impact Factor
Color coding represents risk severity

In the rows of the AI RAMM table (see Figure 6), the application-specific risks, which were defined in the hazard identification, are listed and sorted along the hazard clusters. Here, the quality dimensions defined in the AI Governance & QA Framework are used [15], providing a blueprint to derive measurable AI quality expectations based on the intended use.

This facilitates effective communication along the life cycle. Based on the specific needs and experience of the organization, the detailed assessment along the quality dimensions could be skipped and a simple evaluation of low, medium, or high risk could be performed.

The original RAMM model uses a statically defined relative importance of the CQA, but for AI, the hazard impact, which depends on the hazard level defined in the risk severity matrix, is used. For the hazard impact, the following numbers are used based on the respective hazard level: low (1), medium (3), high (9), very high (18).

During the risk evaluation with the respective stakeholders, the risks defined under the hazard clusters are rated according to the quality dimensions. For the individual score, the risk ratings—marked in gray, e.g., low (1), medium (3), high (9)—are weighted by the HIF per quality dimension. For the total score of a risk, the individual scores per quality dimension are summed. The total score per risk can be used to determine when a mitigation is required and to prioritize the implementation of mitigation measures for different risks.

In addition, the hazard cluster total score can be determined by the sum of the total scores. The hazard cluster total score can be used to evaluate the need for additional controls and prioritization based on the hazard clusters. In addition, the overall score—because it is leveled by the hazard impact—can be used to compare various ML-enabled systems from a risk portfolio approach. This structuring of the AI RAMM provides a compromise between detailed risk evaluation and derivation of comparable scores to prioritize adequate measures.

Risk Control

Based on the completed risk assessment, risk reduction measures can be defined that can be used to reduce the individual risk rating. Typical measures are testing activities, the implementation of additional procedural or technical controls (similar to FMEA-based risk mitigations), or the collection of additional training data. The risk reduction action thereby impacts the individual ratings of the risks according to the quality dimensions. For the implementation of additional controls, it should be considered that these can introduce new risks.

During interactive sessions with respective stakeholders, the RAMM can be run through various iterations until the overall risk is considered acceptable. During these iterations, the proposed color code proves to be a core strength of the RAMM model because it visually highlights individual risks and the effects of risk reduction measures.

For AI systems where the risks cannot be mitigated to an acceptable level via individual risk reduction measures, the sum of risks can be reduced by an adjustment of the AI maturity level. This leads to a reduction of the risk severity level and impacts the overall evaluation and total score.

The adjustment of the AI maturity level can be influenced by redefining the AI autonomy or the AI control design. A mitigation via the adjustment along the X-axes in the risk severity matrix is usually not possible because this directly depends on the use case.

Taking the sum of these measures, the risks can be brought to an acceptable level to complete the risk control cycle.

Risk Review

During the risk review, the full power of the proposed RAMM model becomes apparent. For AI systems moving to greater autonomy and taking over design controls in highly critical areas, the governance and thereby control of the operational phase is the critical factor. The periodic review of risks, refinement, and extension is key to ensure GxP compliance and assure trustworthiness of the system.

Therefore, the periodic cycle of risk reviews depends on the AI Maturity Assessment. During these risk reviews, the RAMM model provides a powerful tool to evaluate observations during normal operations, the impact of potential changes to algorithms, and the impact to the continuous improvement cycles along the AI Maturity Model stages and how to move the process up the hierarchy.

Thus, the RAMM model can also be used to put risks of different AI applications into perspective and to determine what is acceptable for stakeholders and where redesigns should be considered. In addition, given this dynamic setting, insights from similar or adjacent ML-enabled computerized systems may be used to reconsider the risk and risk mitigation strategy.

For instance, if risks are mitigated to a higher degree by one computerized system with controls and mitigations, similar ideas might be used to strengthen the risk strategy of a second system. Hence, the risk review should be performed with a holistic approach, leveraging best practices, process understanding, forward-looking methodology, and critical thinking.

Looking to the future of AI applications in GxP environments, we see iterative risk management cycles as the key concept to enable the use of truly autonomous learning algorithms of AI maturity level VI in a GxP environment.

CONCLUSION

We compiled an industry-specific ML risk and control framework based on the quality risk management process in the ICH Q9(R1) guideline, leveraging four key concepts: the AI Maturity Model [14], *GAMP 5® Second Edition* [10], the AI Governance & QA Framework [15], and RAMM [16]. To this end, we have adapted the RAMM model to facilitate the risk management process.

What we call the AI RAMM model offers two main benefits. First, the multilevel structure allows teams to address AI application-specific risks and their scoring and to define risk mitigation throughout implementation projects. Second, it visually highlights critical areas using easy-to-comprehend color codes, which facilitate risk reviews that gain even higher importance with increasing autonomy and as presentations during audits.

In addition, the AI RAMM model provides organizations with a tool to compare risks across different ML applications and hence foster sharing of ideas, practices, and critical thinking concepts. The approach promotes active learning about risks and enables effective risk monitoring. Our downstream process optimization use case demonstrates the effectiveness of the ML risk and control framework in handling the complexity of ML-related risks in line with the ICH Q9(R1) guideline, exemplifying the conceptual hazard clusters to structure and improve risk oversight.

In conclusion, we can enhance the acceptance of AI usage in regulated areas of the industry by facilitating effective and efficient risk management of AI applications, possibly even in situations when dealing with dynamic online learning and ML operating models. Finally, the prioritization of risk mitigation activities that can yield maximum impact and provide feedback for subsequent risk management iterations are likely to enhance the quality of AI applications and related processes.

Acknowledgments

The authors would like to thank the ISPE D/A/CH (Germany, Austria, and Switzerland) Affiliate subcommittee on AI Validation and ISPE GAMP® Global Software Automation and Artificial Intelligence Special Interest Group (SIG) for their support on the creation of this ML risk and control framework. In particular, we would like to thank Laila Bekhet, Karl Laukenmann, Stefan Münch, Arif Rahman, Nagoor Shareef Shaik, and Michelle Vuolo for their review of this article and their fruitful discussions with the authors throughout the writing process.

References

1. The Stanford Institute for Human-Centered Artificial Intelligence. *Artificial Intelligence Index Report 2023*. Stanford, CA: Stanford University, 2023.
2. US Food and Drug Administration. "Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices." October 2022. www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices
3. Heitmann, M., S. Münch, B. M. Stockton, and F. Blumenthal. "ChatGPT, BARD, and Other Large Language Models Meet Regulated Pharma." *Pharmaceutical Engineering* July/August 2023. https://ispe.org/pharmaceutical-engineering/july-august-2023/chatgpt-bard-and-other-large-language-models-meet
4. US Food and Drug Administration. *Artificial Intelligence in Drug Manufacturing*. Silver Spring, MD: US Food and Drug Administration, 2023. www.fda.gov/media/165743/download
5. US Food and Drug Administration. *Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products*. Silver Spring, MD: US Food and Drug Administration, 2023. www.fda.gov/media/167973/download?attachment
6. European Medicines Agency. Committee for Medicinal Products for Human Use. "The Use of Artificial Intelligence (AI) in the Medicinal Product Lifecycle." July 2023. www.ema.europa.eu/en/use-artificial-intelligence-ai-medicinal-product-lifecycle#current-version-section
7. European Medicines Agency. GMP/GDP Inspectors Working Group. "Concept Paper on the Revision of Annex 11 of the Guidelines on Good Manufacturing Practice for Medicinal Products – Computerised Systems." September 2022. www.ema.europa.eu/en/documents/regulatory-procedural-guideline/concept-paper-revision-annex-11-guidelines-good-manufacturing-practice-medicinal-products_en.pdf
8. US Food and Drug Administration. "Good Machine Learning Practice for Medical Device Development: Guiding Principles." October 2021. www.fda.gov/media/153486/download
9. International Society for Pharmaceutical Engineering. *ISPE GAMP® RDI Good Practice Guide: Data Integrity by Design*. North Bethesda, MD: International Society for Pharmaceutical Engineering, 2020.
10. International Society for Pharmaceutical Engineering. *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)*. North Bethesda, MD: International Society for Pharmaceutical Engineering, 2022.
11. Altrabsheh, E., M. Heitmann, P. Steinmüller, and B. P. Vinco. "The Road to Explainable AI in GXP-Regulated Areas." *Pharmaceutical Engineering* January/February 2023. https://ispe.org/pharmaceutical-engineering/january-february-2023/road-explainable-ai-gxp-regulated-areas
12. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. "ICH Harmonised Guideline Q9(R1): Quality Risk Management." Adopted January 2023. https://database.ich.org/sites/default/files/ICH_Q9%28R1%29_Guideline_Step4_2022_1219.pdf
13. National Institute of Standards and Technology. US Department of Commerce. "Artificial Intelligence Risk Management Framework (AI RMF 1.0)." January 2023. doi:10.6028/NIST.AI.100-1
14. Erdmann, N., R. Blumenthal, I. Baumann, and M. Kaufmann. "AI Maturity Model for GxP Application: A Foundation for AI Validation." *Pharmaceutical Engineering* March/April 2022. https://ispe.org/pharmaceutical-engineering/march-april-2022/ai-maturity-model-gxp-application-foundation-ai
15. Altrabsheh, E., M. Heitmann, FRM, and A. Lochbronner. "AI Governance and QA Framework: AI Governance Process Design." *Pharmaceutical Engineering* July/August 2022. https://ispe.org/pharmaceutical-engineering/july-august-2022/ai-governance-and-qa-framework-ai-governance-process
16. Brindle, A., S. Davy, D. Tiffany, and C. Watts. "Risk Analysis and Mitigation Matrix (RAMM) – A Risk Tool for Quality Management." *Pharmaceutical Engineering* January/February 2012. https://ispe.org/pharmaceutical-engineering/january-february-2012

About the authors

Rolf Blumenthal is a Senior Consultant at Körber Pharma (formerly Werum) and has many years of experience in the pharmaceutical industry. He joined Werum in 1979 and is one of the 15 employees who took over the company after the death of the founder in 1982. Initially, he gained expertise in the management of large manufacturing execution system (MES) software projects. In following years, he headed the development of Werum's MES product, established a consulting division, and started a new division to unlock the added value of data from the pharmaceutical industry. Rolf is a recognized expert with extensive knowledge and hands-on experience in current GMP, US FDA requirements, GAMP® guidelines, and computer validation. He is a member of the GAMP® D/A/CH Steering Committee and the GAMP D/A/CH AI Validation Special Interest Group. He holds a degree in mathematics and computer science from the University of Dortmund, Germany. Rolf joined ISPE in 2002.

Nico Erdmann, PhD, is Senior Manager at Deloitte Germany where he is part of a team dedicated to regulatory and compliance in the life sciences industry, and where he leads the IT quality practice. In this role, he oversees all computerized validation projects, develops validation approaches for new technologies and IT quality frameworks for companies. As part of this role, he develops frameworks for ensuring GxP compliance of ML applications in regulated environments. Nico is a standing member of the ISPE GAMP® GxP-Compliant Use of AI Special Interest Group, has co-published an article on the AI Maturity Model, and has given several presentations on this subject. He holds a doctoral degree in organic chemistry and worked in the pharmaceutical industry before he switched to consulting. He has been an ISPE member since 2019.

Martin Heitmann is a Senior Manager at d-fine. In this role, he transfers process design, data science, and large-scale implementation expertise into ambitious digital transformation projects. His first projects were in the financial industry, where he designed large data pools to apply predictive analytics for rating assessments. As d-fine expanded its operations to other industries, Martin took part in founding the d-fine healthcare unit. In the collaborative pharmaceutical community, Martin is an active member in various knowledge-sharing platforms and leads the ISPE GAMP® Global GxP-Compliant Use of AI Special Interest Group. He holds a Master of Science in business mathematics from the University of Mannheim. He has been a member of ISPE since 2022.

Anna-Liisa Lemettinen is a Business Development Manager at Nagarro GmbH, with more than 20 years of experience in technology projects and digital innovation with specific focus on the life sciences and pharmaceutical industries. With a background in requirements engineering and business analysis, she is dedicated to exploring capabilities of AI and ML in various areas, such as assuring quality and implementing effective risk management approaches. Anna-Liisa is a member of the ISPE GAMP® Global GxP-Compliant Use of AI Special Interest Group (SIG), the ISPE GAMP® Global Software Automation and Artificial Intelligence SIG, and Women in Pharma. She joined ISPE in 2022.

Brandi Stockton is Co-founder of The Triality Group LLC, providing quality, regulatory, and compliance consulting services for the life sciences industry. She has over 20 years of GxP experience, with specialization in computer systems quality and data integrity. Brandi is currently a member of the GAMP® Global Steering Committee, serves as Secretary of the GAMP® Americas Steering Committee, and is Co-Chair of the ISPE GAMP® Global Software Automation and Artificial Intelligence Special Interest Group. She joined ISPE in 2014.

QUALITY CONSIDERATIONS IN DISASTER RECOVERY: A Case Study

By Frank Henrichmann, Oliver Herrmann, Maximilian Stroebe, PhD, and Marcus Schwabedissen

Due to the growing digitalization of the industry, we are highly dependent on information technology (IT) systems and data. The basic ability to execute our pharmaceutical business and decision-making processes relies on the permanent availability of these IT systems and data to ensure compliance and efficiency of our business operations. But numerous factors—including criminal activities, political unrest, and environmental hazards—have made disaster recovery (DR) and business continuity planning essential.

A GROWING NEED FOR DISASTER RECOVERY PLANS

Cybersecurity attacks have been on the rise for many years, with ransomware and phishing being the top threats to our industry. A 2023 survey found that 66% of organizations experienced at least one ransomware attack [1]. How can the life sciences industry become more resilient against those attacks while acknowledging that 100% security cannot be established?

Appendix O10, "Business Continuity Management," and Appendix O11, "Security Management," in the *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* provide excellent guidance for requirements and measures to prevent security incidents from happening and keep the business operational during a disaster [2]. Most companies rely on their backup and restore capabilities for their DR strategy; therefore, the backup setup, verification, and monitoring described in Appendix O9, "Backup and Restore," should be considered [2].

Other standards also provide detailed guidance:

- ISO/IEC Standard 27000:2018 provides an overview of information security management systems [3], including ISO 27031, A Standard for IT Disaster Recovery.
- ISO/IEC Standard 22301:2012 sets out the requirements for a business continuity management system [4].

DR, business continuity, and backup and restore are closely connected and need to be managed throughout the entire system and data life cycle (see Figure 1).

DR aims to anticipate and assess the impact of disasters and to build strategies and plans for how to recover from such disasters. In this context, a disaster may be related to IT (e.g., cybersecurity incident), staffing (e.g., pandemics), or facilities (e.g., natural disasters). Business continuity addresses how to keep the business processes operational in case of any disaster. In case of an IT-related (including IT facilities) disaster, the backup and restore capabilities are typically key to restoring IT systems, data, and services.

However, cybercriminals are increasingly designing their ransomware code as a time bomb to hinder the company from easily restoring their IT systems and data. Rather than encrypting data immediately after it gets past the corporate firewall, it begins to infect the data over time. Days, weeks, or months later, when the infected data has been backed up, it initiates the encryption of the corporate data. As the backup is also infected, it cannot be restored easily and may encrypt already restored data or systems.

THE HUMAN FACTOR

Humans tend to believe that disasters "only happen to other people." And even if a disaster did happen to them, they are convinced that they would know how to deal with it. This combination of over-optimism, normalcy bias, and tendency to overvalue known short-term costs and under-value unknown long-term rewards is

referred to as the "preparedness paradox" and is reflected in sentences like:

- "Why would anyone attack us? We are too small/insignificant/etc.!"
- "We have state-of-the-art IT protection. We are safe."
- "If the data center blows up, I'll just walk over to the next IT store, buy new equipment, and bring it all back in no time."
- "If an IT system goes down, we can always restore it from the backup in no time at all. No further planning is required."
- "What do you mean when you say, 'We need to test if we can restore data/systems from the backup?' We are using a market-leading software, and it has not given us any errors or alarms. It works!"
- "If the IT goes down, we just go back to paper. It worked in the past, didn't it?"

This human trait often leads to:

- Lack of time, resources, and willingness to take this seriously and contribute (e.g., "This will never happen, so this is a waste of time.")
- DR or business continuity plans (BCPs) that are not fit for purpose (e.g., badly designed or not up to date)
- Lack of robust testing of the plans (e.g., scenarios are too simple, assumptions are too positive, everything is simulated and not tested, or tests are always postponed due to "more urgent business")
- Missing concepts for processing paper records and reintegration of these records into the restored computer systems

This is also reflected in the fact that only 50% of all companies test their DR annually or less frequently, whereas 7% do not test their DR at all [5]. But when a major security incident leads to widespread system issues and data loss strikes, what are the best practices? What are the benefits of appropriate planning? And what are potential challenges from a quality perspective?

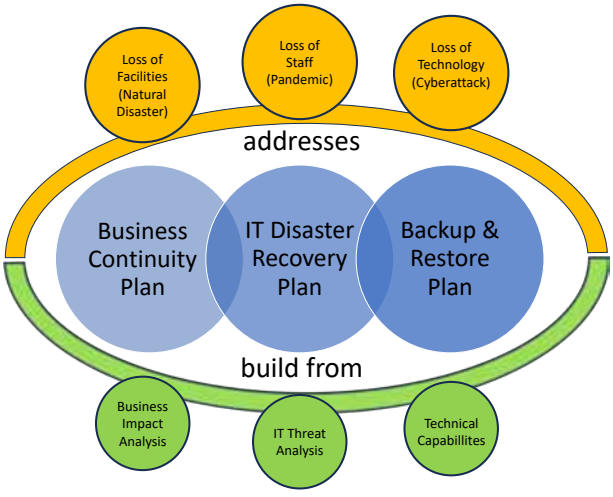
In this article, the authors have created, based on several DR scenarios they have been involved in, a hypothetical case study of a successful ransomware attack to highlight potential pitfalls and provide guidance on how to restore regular business and compliance. However, the guidance can easily be adapted to other incidents that lead to significant data loss or system unavailability.

THE IMPORTANCE OF PLANS

Every regulated organization should have adequate DR and BCPs. These plans should cover a variety of potential disasters and provide detailed guidance on how to operate during a disaster and recover back to normal processes as quickly as possible. Furthermore, required roles and responsibilities should be defined and individuals to fill those roles identified.

Organizations that do not spend the necessary time and resources on creating and maintaining these plans on an ongoing basis have already fallen for the first pitfall in DR. Without such plans, the significant amount of confusion that invariably happens once a disaster strikes is prolonged unnecessarily.

Figure 1: Types of plans and threats they address.



The organization may be paralyzed at the IT level and communicate through unusual channels, e.g., via social networks. But well-designed plans and robust communication can reduce the duration and intensity of this period significantly. Without a plan, communication channels and roles and responsibilities are unclear. Most organizations may not know what to do, how to communicate, or how to get further information.

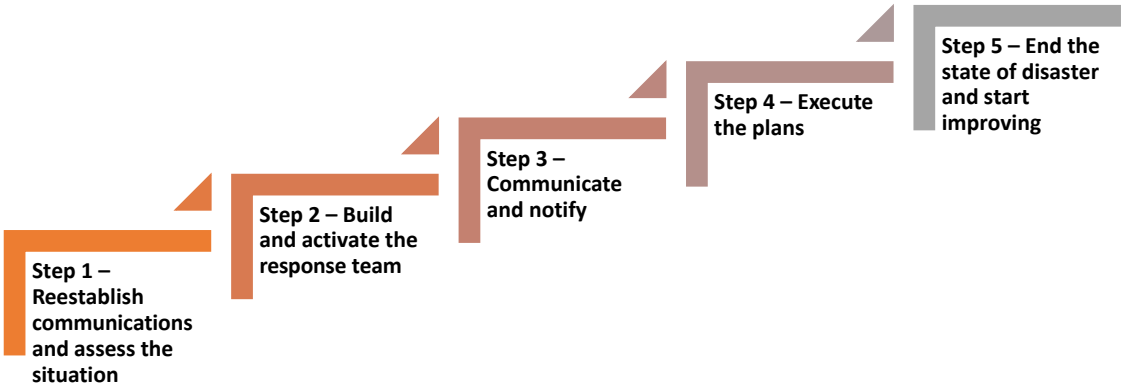
DR and BCPs are worthless if they cannot be accessed in a disaster. Separate, secure, and accessible storage should be established for these documents, and supporting documentation (e.g., the business impact analysis or the risk assessment) should also be stored in that location. The value of DR and BCPs can also be diminished if they are not frequently reviewed and adequately tested to ensure they are fit for purpose.

The level of preparedness for such disasters can be assessed through internal audits that focus on DR and/or ransomware readiness. The Information Systems Audit and Control Association (ISACA) provides focused audit programs like the "IT Business Continuity/Disaster Recovery Audit Program" for these areas [6]. These audits may verify that the design of the IT landscape is resilient to widespread ransomware attacks, e.g., via an appropriate network architecture, as well as the existence and quality of plans and procedures.

A HYPOTHETICAL CASE STUDY: SETTING THE SCENE

Disasters can strike your organization in many ways, and every disaster is unique and requires unique recovery activities. Common to all IT disasters is that data and systems are either lost, not available, or stolen. This article does not consider natural disasters and similar incidents where the health and safety of the organization's staff are directly at risk. The case study that we want to use as an example throughout the article is a midsized pharmaceutical company that has been hit by a ransomware attack.

Figure 2: Steps in recovering from an IT disaster.



The ransomware encrypted most of the connected endpoint devices, infected system backups over a period of three months, and encrypted most servers in the organization. Also, data that was stored on cloud infrastructure had been encrypted. Electronic communication via email or collaboration platforms was not possible. The company has BCPs and an IT DR plan that is available on every site as a paper printout. A permanent disaster hotline is available for all staff. In our hypothetical case study, the organization followed the following DR steps (see Figure 2).

Step 1: Reestablish Communications and Assess the Situation

As a very first step, the organization needs to evaluate the extent and impact of the IT disaster. To enable any kind of DR activities, staff must identify the affected systems, data, and infrastructure. To achieve this, it is critical that key decision-makers, as outlined in the relevant plans, are informed of a potential disaster as quickly as possible and have the means to establish communications quickly and permanently without having to rely on company resources that may be unavailable in a disaster.

It is critical that the IT, quality, and relevant business, legal, and human resources departments are included in these early communications and assessments, as not only the impact on technology must be determined but also the potential downstream impacts on regulatory compliance, product quality, data integrity, patient safety and privacy, financial stability, and company reputation.

Once the damage has been contained by isolating affected systems to prevent further damage and after the extent of the disaster has been roughly established, the "responsible person" needs to declare the disaster. This may be the CEO, or other leadership, but it should be as outlined in the applicable plan, with backup leaders as needed should someone be unavailable.

Declaring the disaster is important because the company may suspend and/or adapt processes for the duration of the disaster, e.g., falling back on paper documentation and processes for impacted IT or business processes. The initial investigation must identify the technical root causes of the disaster so that any vulnerabilities or weaknesses that contributed to it can be considered when planning and making decisions on what to do next.

The leadership of the organization now needs to determine and balance the following aspects:

- How to enable business and reduce or limit financial loss for the organization (e.g., through short-term workarounds)
- How to restore manufacturing to produce critical products to ensure patient safety
- How to manage potential technology and IT supply chain constraints
- If and how the disaster impacts regulatory compliance
- How to handle data privacy implications (e.g., for data theft)
- How to meet legal/regulatory obligations (e.g., shareholder notification)

In our hypothetical case, communication could quickly be reestablished because the board of directors kept a list of the up-to-date contact information of the key decision-makers and other critical staff in a safe, "break-glass" location. That allowed key communications to be restored via social media, and meetings could be organized and conducted.

The initial assessment showed that affected systems included:

- Manufacturing systems, including the manufacturing execution system (MES)
- Laboratory systems, including the laboratory information management system (LIMS)
- Document management systems, including all standard operating procedures (SOPs)
- Pharmacovigilance system
- Email and collaboration platforms, intranet, and extranet
- IT systems for backup, including the configuration management database (CMDB) and service desk
- Financial systems

The root cause was a ransomware attack that was introduced to the organization by unknown means. Further forensics are

initiated to identify the root cause. After careful consideration, it was decided not to pay the ransom and use the services of a prequalified IT security service provider to analyze the attack, determine the exact circumstances that introduced the ransomware to the organization, and help recover the data and systems.

Step 2: Build and Activate the Response Team

As a next step, the organization needs to assemble a team of experts responsible for managing the recovery process and assign roles and responsibilities to team members. With the team, the organization needs to prioritize the systems and data recovery in more detail and identify potential obstacles.

In our hypothetical case, the company made the following high-level decisions for response teams. Dependencies between the workstreams were identified and tasks were worked on in parallel wherever possible. The response team leaders aligned themselves in daily meetings.

Response team: infrastructure

- Priority 1: Establish a secure infrastructure environment, including backup services.
- Priority 2: Reestablish email and collaboration platforms, intranet, and extranet.
- Priority 3: Reestablish the CMDB and service desk.

Response team: applications and systems

- Priority 1: Reestablish the MES.
- Priority 2: Reestablish the LIMS.
- Priority 3: Reestablish the pharmacovigilance system.
- Priority 4: Reestablish the financial systems.
- Priority 5: Reestablish the document management systems, including all SOPs.

Response team: quality

- Priority 1: Assess risk to data integrity, product quality, patient safety, and regulatory compliance.
- Priority 2: Document the disaster, including all decisions and actions.
- Priority 3: Stand up support teams that establish basic processes for recovery activities.

Response team: legal

- Priority 1: Assess legal obligations and restrictions, including data privacy, financial, and other regulations.

Step 3: Communicate and Notify

It is crucial to inform relevant staff of the disaster and the next steps to be taken to reestablish normal operations as soon as possible as well as provide potential instructions for end users. This can, for example, be communicated via established support channels, if still available, or via announcements over a disaster hotline that has been established before the disaster.

Furthermore, the established group of decision-makers must decide on the potential need to communicate the disaster externally (e.g., to regulatory authorities, partners, or customers). All external communication, including to the media, must be tightly controlled and managed (e.g., for shareholder information).

In our hypothetical case, a toll-free disaster hotline number was available and was used to relay information and general instructions to the organization. Through this line of communication, which was supported by social media, town hall meetings could be organized to provide further information to the employees.

Regulatory authorities should be informed that the company will be unable to produce essential products that some patient groups depend on. The board of directors should inform all impacted partners. Communication with the public, including customers, is initiated, and overseen by the board of directors and managed/executed by the public relations department.

Step 4: Execute the Plans

By their very nature, BCPs and IT DR plans must be very flexible because disasters can strike an organization in many ways and can take many different forms. At the same time, the plans need to outline technical dependencies clearly and be based on the business impact analysis and the risk assessment that was done when the plans were created. With support from subject matter experts, the response teams now need to decide which parts of the plans must be implemented and build a strategy for recovering services and systems.

This is not the time for parts of the organization that did not contribute to plan development to question the plan's basic structure. Any changes to the established plans, e.g., reprioritization of recovery activities, may require an impact and risk assessment to avoid undesired effects on the overall recovery activities and should require approval by the organization's senior management.

The appropriate quality functions should be involved throughout the entire execution of BCPs and IT DR plans. Even in case of a disaster, quality and regulatory compliance must not be neglected. In such situations, quality functions need to be "enablers" that help establish critical documentation and records during recovery activities. The documentation will not be perfect but should be sufficient to allow justified decision-making on the release of systems and data that could impact product quality, patient safety, or data integrity.

Considering the challenges the organization is facing in such times, flexibility and critical thinking by everyone is absolutely required. In our hypothetical case, the analysis of the attack showed that:

- The attack already happened months ago and infiltrated all backups.
- The attack vector was phishing.
- The preventive technical controls were ineffective and not well maintained.

- The historically grown infrastructure was not designed to contain such an attack to a section of the IT landscape.
- The IT security service provider can decrypt the affected files with special tools and software re-engineering.

The BCP and IT DR plan provided the required order for the recovery of systems and data. The quality organization faced the following challenges that had not been considered in the plans:

1: Drug shortages

"Our company produces important (potentially life-saving) products that some patient groups depend on. What is the best way to avoid drug shortages without sacrificing product quality?"

The BCP for the manufacturing process outlines and documents alternative ways to operate in case IT systems are unavailable. The approach was evaluated (including a risk assessment by quality assurance), adapted based on the nature of the disaster and the recovery planning, and discussed with applicable regulatory authorities as outlined in the European Medicines Agency's regulatory guidance on drug shortages [7]. Once implemented, additional reviews, verifications, and checks are performed and documented to ensure data integrity, patient safety, and product quality are not at risk.

"Our company produces important (potentially life-saving) products that some patient groups depend on. What is the best way to avoid drug shortages without sacrificing product quality?"

2: Documentation for audits and inspections

"How do we document the incident, the root cause, and the sequence of the events in such a way that it can be presented and defended in audits and inspections?"

Processes that are especially timebound like pharmacovigilance can be a significant challenge because regulatory timelines must be met during the disaster.

It was decided that a dedicated resource in quality would maintain a chronological issue log containing all activities and decisions. All quality and IT staff (including the IT security service provider) must copy this resource on all relevant communications. All created documentation must consider potential needs for confidentiality.

3: Interim processes

"How do we provide the organization with interim processes until the SOPs from the document management system have been restored?"

Interim processes and supporting templates are created by the quality organization and provided via a cloud storage provider. These processes are abbreviated, focusing on the essentials, and not extensively reviewed but approved by senior quality executives. The following order has been established for the creation of quality processes:

- Infrastructure qualification
- IT change control
- Validation of computerized systems

Training is done virtually, and attendance is recorded manually. In parallel, non-IT-related processes must be reestablished or restored (e.g., for manufacturing and quality control of medical products). The prioritization should be based on patient safety, product quality, and data integrity.

4: Data integrity

"How do we maintain data integrity during and after the disaster?"

Because alternate ways to operate involved the creation and/or processing of paper documentation, a task force was created to ensure appropriate handling of the paper records throughout the entire data life cycle and to develop a strategy to integrate the data once the IT system is available again.

This approach, already documented in the BCP and the business process requirements, was adapted for every system and business process individually, based on the specifics of the disaster (e.g., anticipated time to full system recovery).

Processes that are especially timebound like pharmacovigilance can be a significant challenge because regulatory timelines must be met during the disaster. After the disaster, all data must be integrated into the restored system to allow the processing of follow-up information and the ongoing analysis and evaluation of product safety.

5: Qualification of IT infrastructure

"How do we record the qualification of the IT infrastructure, including potential changes to the architecture and design to prevent such incidents going forward?"

The recovery activities start immediately based on security recommendations by the IT security service provider and are recorded informally, covering:

- Date and time of the activity
- Specification and configuration of the infrastructure
- Required verification activities
- Name of the person performing the activity

The quality department will establish an abbreviated process and templates for infrastructure qualification to be used going forward. When published, the process will be executed retrospectively and based on risk for already established infrastructure at that point in time. All created records must consider potential needs for confidentiality. The usage of tools and automation, where possible, is highly recommended.

6: Decryption tools

"How do we qualify the tools used to decrypt the data and systems? How do we know the data is correct and complete and the systems are fit for the intended use (also considering the changes to the underlying infrastructure)?"

Existing tools of the prequalified IT security service provider are used as is and qualified retrospectively. The qualification will leverage the existing vendor documentation and technical integrity checks to the extent possible. The testing of the tools focuses on:

- Identifying unencrypted files, databases, and servers
- Encrypting these items with the original ransomware in a controlled environment
- Decrypting them with the existing tools of the IT security service provider
- Verifying that the items and data are the same after processing and free from malware

If possible, the qualification of the recovery tools will be completed before the recovered systems and data are used in production again. All created documentation must consider potential needs for confidentiality and IT security. Systems that do not function as intended due to tighter security will be prioritized and investigated. All decrypted systems that are used productively without the qualification of the tools completed will be reviewed and released by the process owner and senior quality management.

7: Ransom situations

"How do we deal with data loss, e.g., data or systems that cannot be restored?"

For every logical group of lost data, a corrective and preventive action will be issued to investigate how the data was lost, the risk or impact of this data being lost, and measures that can be taken to prevent reoccurrence. Examples of data loss risks and impact include regulatory noncompliance (e.g., retention period), inability to recall the product, incomplete drug safety data, and lost business and financial impacts. Again, all created documentation must consider potential needs for confidentiality and IT security.

A similar approach could (and should) be used in scenarios where the ransom is paid and the key for decryption is provided.

To pay or not to pay

On average, 46% of the companies that were hit by a ransomware attack in 2022 paid the ransom, which was, on average, around $1.5 million US [1]. That makes ransomware a lucrative business model for cybercriminals, but law enforcement agencies recommend not paying the ransom. In fact, paying the ransom could even be illegal, because it could be violating the US Office of Foreign Assets Control's regulations or other similar regulations [9] or interpreted as funding terrorism under the United Kingdom's Terrorism Act [10].

Still, in many cases, it is easier, faster, and cheaper to pay the ransom than to recover from backup. The basic assumption is that if organizations pay the ransom, the attackers will provide a decryption tool and withdraw the threat to publish any potentially stolen data. However, payment does not guarantee all data will be restored. In reality, on average, only 65% of the data is recovered, and only 8% of organizations manage to recover all data [8]. After all, cybercriminals are not necessarily IT experts or software developers that you can trust.

In fact, encrypted files are often unrecoverable because the attacker-provided decryptors may crash or fail. In such cases, you may need to build a new decryption tool by extracting keys from the tool the attacker provides. This raises significant quality and data integrity concerns, as already outlined previously in step 3. Finally, "there is no honor among thieves"—paying a ransom may increase the likelihood of repeat attacks on an organization. The cybercriminals now know that your system is a good target and that you will pay a ransom.

Step 5: End the State of Disaster and Start Improving

When a predefined recovery level has been reached (e.g., all critical systems recovered), the state of disaster should be formally ended. This can be done for entire organizations or for individual areas of the business (e.g., when systems and/or data have been restored) so that the associated processes can be executed as they were before the disaster.

At that time, a thorough analysis of the incident should be performed to identify further areas of improvement. By this time, your organization will have a good estimate of the losses the company has suffered due to the incident. Based on the analysis, losses, and risk assessment, an improvement plan should be developed that may include:

- A review of processes to create and update BCPs and IT DR plans
- Technical and design controls to increase security, such as:
  - Hardening of infrastructure
  - Zoning of networks
  - Creating a DR instance of critical systems
- Organizational and procedural controls, such as:
  - Storing of BCPs and IT DR plans outside of the company network
  - Emergency contact information

The plan's outcome and analysis should be considered in the remaining recovery activities and the implementation of all new systems and infrastructure going forward.

BEST- AND WORST-CASE DISASTER RECOVERY APPROACHES

What if a company is not as well prepared as the one in our hypothetical case study? Table 1 contains best-case approaches as outlined in the case study and worst-case alternatives and their consequences. This list is not exhaustive and is meant to encourage critical thinking and discussion around DR and business continuity.

CONCLUSION

As Scottish poet Robert Burns said: "The best-laid schemes of mice and men go oft awry." However, if plans are created with the necessary care, they can be invaluable in an IT disaster. They reduce the initial state of confusion and allow for the prioritization of activities based on already performed risk assessments. Preselected and prequalified service providers for forensic analysis and data restoration may further reduce downtimes and speed up recovery activities.

The challenges to the quality organization during DR are many. Often activities are done in parallel, processes may be unavailable or not fit for purpose, and documentation may not be as controlled as it was when all systems were available. A pragmatic approach that focuses on product quality, patient safety, and data integrity and that is based on risk and critical thinking is essential.

Depending on the nature of the disaster, the quality organization may need to:

- Support the teams in the creation of required processes to support recovery activities.
- Support infrastructure qualification and computer system validation activities for systems that are restored or rebuilt.
- Assess data integrity of restored systems and data, including data integration activities after the system is restored.
- Support risk-management activities to ensure the effectiveness of workarounds and other short-term measures.
- Document the disaster, the subsequent analysis, the root cause, the corrective actions, and the lessons learned.

Table 1: Best- and worst-case scenarios for prepared vs. unprepared companies.

Item	Best-Case Approach	Worst-Case Approach
Availability of DR plan and BCPs	The company has BCPs and an IT DR plan that are available on every site as a paper printout.	The company's BCPs and IT DR plans are encrypted and unavailable. It takes several days to piece these together based on outdated drafts, meeting notes, and other materials that were not encrypted.
Initial Communications	Communication can quickly be reestablished through contact information in a "break-glass" location. This allows key communications to be restored via social media, and meetings can be organized and conducted.	The contact information is distributed (e.g., on individual cell phones) or unavailable. It takes weeks to contact all the key decision-makers and contributors. Meetings with all relevant contributors are difficult to organize. Decisions taken without all contributors' input may be revised later, adding to the already existing confusion.
Further Communications	The already established toll-free number allows sending information and instructions to the employees. A town hall meeting was organized to explain the situation and to explain the next steps. The controlled external communication meets legal requirements (e.g., for shareholder information) and limits the damage to the company's reputation.	Information and instructions cannot be relayed to the employees, resulting in anxiety and panic. External communication is not tightly controlled, leading to legal issues with shareholders and authorities, excessive damage to the company's reputation, and loss of potential business.
Initial Assessment	Communication was reestablished quickly, and an initial assessment and high-level root cause analysis was completed. The extent of the disaster was quickly established, and the necessary actions and steps were planned and initiated.	Due to lack of communication, it takes several days to establish an initial assessment and high-level root cause analysis. Actions and next steps are planned based on available information, but actions and priorities change as more information becomes available over time.
Prequalified IT Security Service Provider	A specialized, qualified, and trustworthy IT security service provider can be brought in quickly to support DR with technical expertise, forensic services, and consultancy.	An IT security service provider is identified based on an ad hoc web search. The negotiations and contractual agreements are accelerated but still take several days. Later, it is observed that the provider was unfamiliar with GxP environments and too expensive.
Prioritization	The BCPs and IT DR plans provide the required order for the recovery of systems and data based on predetermined technical dependencies and risk assessments.	After the BCP and IT DR plan have been recovered, the prioritization is questioned, as technical dependencies and business requirements are not up to date. The underlying thought processes and risk management is lost.
Documentation of the Incident	A chronological issue log containing all activities and decisions is created contemporaneously during the DR activities. It helps to explain what happened in audits and inspections and to justify decisions taken.	The absence of preliminary documentation potentially results in audit findings, leading to a subsequent initiative to generate this documentation retrospectively. However, this is an extraordinarily challenging task, as relevant information is no longer accessible.
Processes	Interim processes and supporting templates are created by the quality organization and provided via a cloud storage provider. Training is done virtually, and attendance is recorded manually.	Interim processes are not created as the organization expects to have their SOPs available again soon. In the meantime, recovery activities are performed without established processes. Speed is valued higher than following a process.
Data Integrity	A task force was created to ensure appropriate handling of the paper records throughout the entire data life cycle and develop a strategy to integrate the data once the IT system is available again.	Data and records are captured, processed, used, and documented without structure. When relevant systems are available again, there is no concept for data reintegration. Some of the resulting data integrity issues become impossible to resolve.

Every disaster is unique, and every organization needs to define its strategy and plans. The measures and controls described in this hypothetical case study may not be suitable for every organization. This case study provides a realistic disaster scenario and demonstrates the value of being prepared and having appropriate plans.

The internal audit program ensures regular reviews of business continuity and DR preparedness and compliance with company expectations. In our scenario, this was the case, and these plans were created using critical thinking that accepts that disasters will strike at some point in time.

For our hypothetical company, we can state that they were very well prepared and decisive. They did not simply focus on IT DR but had roles and responsibilities, priorities, and tasks that were planned beyond what was needed. This significantly contributed to getting the situation under control.

References

1. Sophos. "The State of Ransomware 2023." May 2023. https://assets.sophos.com/X24WTUEQ/at/c949g7693gsnjh9rb9gr8/sophos-state-of-ransomware-2023-wp.pdf
2. International Society for Pharmaceutical Engineering. *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)*. North Bethesda, MD: International Society for Pharmaceutical Engineering, 2022.
3. ISO/IEC Standard 27000:2018. "Information Technology — Security Techniques — Information Security Management Systems — Overview and Vocabulary." February 2018. www.iso.org/standard/73906.html
4. ISO/IEC Standard 22301:2012. "Societal Security — Business Continuity Management Systems — Requirements." May 2015. www.iso.org/standard/50038.html#:~:text=ISO%2022301%3A2012%20specifies%20requirements%20to%20plan%2C%20establish%2C%20implement%2C,and%20recover%20from%20disruptive%20incidents%20when%20they%20arise
5. Computing Research. "When Plan B Goes Wrong: Avoiding the Pitfalls of DRaaS." June 2021. https://iland.com/wp-content/uploads/2021/10/Whitepaper-iLand-Zerto-vs3.pdf
6. Information Systems Audit and Control Association. "IT Business Continuity/Disaster Recovery Audit Program." 2021. https://store.isaca.org/s/store#/store/browse/detail/a2S4w000004KoEfEAK
7. European Medicines Agency. "Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)." July 2019. www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf
8. Gartner. "When it Comes to Ransomware, Should Your Company Pay?" 10 October 2021. www.gartner.com/en/articles/when-it-comes-to-ransomware-should-your-company-pay?
9. US Department of the Treasury's Office of Foreign Assets Control. "Advisory on Potential Sanctions Risks for Facilitating Ransomware Payments." October 2020. https://ofac.treasury.gov/media/48301/download?inline
10. Terrorism Act 2000. www.legislation.gov.uk/ukpga/2000/11/section/17

About the authors

Frank Henrichmann, Senior Executive Consultant at QFINITY, is an expert in quality management, computer system validation, and compliance, especially in clinical trials and pharmacovigilance. He has over 22 years of experience in planning, development, execution, documentation, and auditing of strategies, projects, and measures for GxP-regulated environments. In his current position, he helps life sciences companies and supporting technology providers find innovative answers to the quality and validation challenges created by operating in a highly regulated industry. Frank co-authored the *ISPE GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data.* He is a member of the GAMP® Editorial Review Board and the Knowledge Network Council and is Secretary of the global GAMP® Steering Committee. He also contributed to the *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* as a Chapter Lead and is an ISPE-certified GAMP® Trainer. He joined ISPE in 2001.

Oliver Herrmann is Managing Director of QFINITY, which he founded in 2004 with the vision to combine process management with the requirements for the validation of computerized systems and to offer this package as part of an integrated service portfolio. Oliver has been significantly involved in the planning, development, execution, and auditing of strategies, projects, activities, and procedures for GxP-regulated environments for more than 20 years. His expertise encompasses the full spectrum of methods, principles, and software tools used in the pharmaceutical and medical device industries. He has a degree in applied computer science and is an ISACA-Certified Data Privacy Solutions Engineer, a Certified Scaled Agile Framework Practitioner, and a Microsoft-Certified Systems Engineer. His experience has made him a much sought-after presenter for industry events all over the world. He has been an ISPE member since 2002.

Maximilian Stroebe, PhD, Senior Manager at Janssen Vaccines and Prevention, is an expert in data integrity, computerized system validation, and quality management. He has 19 years of experience in commercial and investigational medicinal products manufacturing and in all aspects of clinical trials at several major pharmaceutical companies in Switzerland, Germany, and the Netherlands. In his current role, he leads the quality oversight team for computerized systems, equipment, and facilities of a biotechnological pilot plant and the related quality control laboratories. Max co-authored the *ISPE GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data* and has presented at several ISPE Annual Meetings. He has been an ISPE member since 2013.

Marcus Schwabedissen is Chief Operating Officer, consultant, trainer, and auditor for QFINITY, a consulting firm for risk-based quality management and validation of computerized systems. He has 25 years of experience in the life sciences industry in quality management systems and the validation of computerized systems in the GxP environment. He has held various positions during his career, including IT manager for a global contract research organization (CRO) with responsibility for offices in Frankfurt, Munich, and Freiburg; head of IT and validation at the Coordination Center for Clinical Trials at Heidelberg University Hospital; and head of global technological quality management and of a quality assurance computer technology auditing group at a leading global CRO. He holds a degree in agricultural engineering with a focus on environmental management. Previously, he worked as an IT consultant and database designer. He joined ISPE in 2007.

THE USE OF INFRASTRUCTURE as Code in Regulated Companies

By Anders Vidstrup and Anette Westphal

IT infrastructure has traditionally been provisioned using a combination of scripts and manual processes. This manual approach was slow and introduced the risk of human error, resulting in inconsistency between environments or even leaving the infrastructure in an unqualified state. In this article, we investigate some fundamental advantages of using Infrastructure as Code (IaC) for provisioning IT infrastructure.

Historically, scripts were stored in version control systems or documented step-by-step in installation guides. Often, the person writing the installation guide was not the same person following it or executing the scripts. The cloud introduces IaC as a provisioning method. IaC is a means of provisioning and deploying infrastructure using development/operations processes. In combination with version control and automation, IaC enhances quality as it relates to compliance and operational stability.

As stated in *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)*, "IaC enables organizations to automate the provisioning of infrastructure, reducing the risk of human errors. Infrastructure code is subject to configuration management ensuring that all code changes are traceable. Infrastructure code development is subject to risk-based software development practices that ensure code is developed in accordance with a life cycle approach including verification prior to deployment" [1]. Hence, IaC provides rigor, clarity, and reliability, thereby improving quality.

WHAT IS IaC?

According to the National Institute of Standards and Technology (NIST), IaC is "the process of managing and provisioning an organization's IT infrastructure using machine-readable configuration files, rather than employing physical hardware configuration or interactive configuration tools" [2]. Section 19.2.4 of the *GAMP® 5 Second Edition* describes the GAMP approach to IaC: IaC is software for managing infrastructure, so it is considered GAMP software category 1. However, because it is still code, it should be managed in a fashion similar to application code. It should be stored in a version management or source control system that logs a history of code development, changes, and bug fixes [1].

Figure 1: Simple IaC template.

```
{
   "Resources" : {
   "Name-of-your-resource" : {
   "Type" : "resource type"
   }
   }
}
```

TEMPLATES OR CODE FOR IMPLEMENTING IaC

There are template-based and code-based options available for implementing and managing IaC. Templates enable developers to describe and create resources in an orderly and predictable fashion. Resources are written in static text files using JavaScript Object Notation (JSON) or Yet Another Markup Language (YAML) format (see Figure 1).

The templates require a specific syntax and structure that depends on the types of resources being created and managed. The programmer creates the resources in JSON or YAML with any code editor, checks it into a version control system, and then provides it to a service that interprets the template and provisions the specified resources in a safe, repeatable manner based on the supplied template.

Figure 2: Simple IaC code.

```
export class HelloWorldInfra extends Stack {
  constructor(scope: App, id: string, props?: StackProps){
    super(scope, id, props);

    /* Create the following resources */
    new Resource(this, 'MyFirstResource', {
      parameter: true
    });
  }
}
```

If a developer needs to make changes to the running resources, they update their template and trigger a redeployment. Optionally, before changes are applied to the resources, they can generate a change set, which is a summary of their proposed changes. Change sets enable a programmer to see how their changes might impact the running resources, especially for critical resources, before implementing them.

A programmer can use a single template to create and update an entire environment or separate templates to manage multiple layers within an environment. This enables templates to be modularized and provides a layer of governance that is important to many organizations. When a programmer creates or updates resources, events are generated showing the status of the configuration. If an error occurs, resources can be rolled back to the previous state. In addition, some cloud providers offer a software development framework to model and provision the cloud application resources using familiar programming languages such as TypeScript, Python, Java, and .NET.

The code in Figure 2 generates the same kind of template seen in Figure 1. These development kits are popular with programmers and leverage the same cloud resource provisioning engine used by the template approach, meaning infrastructure resources are provisioned in the same safe, repeatable manner.

Developers can often leverage their existing integrated development environment—tools like autocomplete and inline documentation—to accelerate development of IT infrastructure. With the code-based approach, a programmer's IT infrastructure can be as testable as any other code they write, and unit tests can be created before any deployment. The main difference is that a template is a static description of the required resources, whereas code can include logic to control the resources requested.

REGULATORY BACKGROUND FOR HOW TO MANAGE IaC

Regulations do not explicitly mention IaC. The primary regulatory requirement toward IT infrastructure is stated in the European Medicines Agency's Concept Paper on the revision of Annex 11 of the guidelines on Good Manufacturing Practice for Medicinal Products – Computerised Systems: "IT infrastructure should be qualified" [3]. According to the European Union's GMP requirements, the definition of qualification is the "action of proving that any equipment works correctly and actually leads to the expected results" [4]. Good IT and software engineering practices should be followed, as described in section 19.2.4 of the *GAMP® 5 Second Edition*, Infrastructure Automation [1].

IMPLEMENTATION OF IaC PROVISIONING METHOD

In the traditional provisioning method, the command line instructions are written in the step-by-step installation guide, which, with the introduction of IaC, has turned into a code-based, automated process to be used repeatedly. Consequently, it is essential that responsibilities and principles have been defined from an overall perspective on how to manage IaC.

Shifting Responsibility

Introducing IaC might require a shift in responsibility between the IT infrastructure provisioning and the software development department. If they are separate departments, merging the departments should be considered; hence, enabling the use of DevOps processes. Cloud services enable programmers to provision resources on demand. There is no longer a need to create a ticket for a request that infrastructure be provisioned by another team and waiting weeks or months for it to be made available. Self-service is the new normal.

Cloud adoption is an opportunity for digital transformation, but that must include revisiting these old organizational structures, operating models, and standard operating procedures and introducing a shift in responsibility. Too often companies retain their old, familiar ways of working and just apply them to the cloud. Some organizations still implement ticketing processes even to provision cloud resources, as this is seen as a way to demonstrate control.

In addition, more companies are moving from project-based to product-based operating models and adopting an agile methodology instead of a waterfall methodology. The same control objectives still exist, but IaC facilitates new ways to achieve them. For example, rather than writing, reviewing, and approving an installation and configuration test script for manual execution, a programmer writes, reviews, tests, and approves an IaC template for automated provisioning. All the changes mentioned previously should only be made in a controlled manner in accordance with a defined procedure, supported and enforced using appropriate tools.

IaC Competencies

When organizations shift internal responsibilities, it also becomes necessary to update employee roles and responsibilities, which requires staff to learn new competencies. These organizational implications are relevant when using cloud in general—but even more essential to consider as part of introducing IaC. Thus, staff training is needed.

All involved employees must have appropriate qualifications in both the technologies used and quality. Thus, qualifications should consist of a combination of education, experience, and continuous training. Engineering teams will obviously be trained in IaC, but quality management roles also need at least a high-level understanding of the technology and how control objectives are achieved through automation.

IaC Coding Principles

To ensure both operational stability and quality, it is recommended that organizations prepare some general principles for implementing, using, and operating IaC, such as:

- IaC scripts should be versioned, tested, reviewed, and approved based on criticality. Information is maintained in tools, and controls are defined in workflows.
- IaC provisioning should be the same in respective environments once they have been finally approved.
- How to remove deprecated components should be defined.
- Handling of confidential information should be considered.
- Repeatability should be ensured.

BUILDING BLOCK QUALIFICATION

The IaC building block concept, as mentioned in *GAMP® 5 Second Edition*, is an approach to qualifying individual components or combinations of components, which can then be put together to build the IT infrastructure and thus use a "one qualification, many deployments" approach [1].

The benefit of this approach is that a programmer can qualify an instance of a building block once and assume all the other instances will perform the same way, reducing the overall effort across applications. This approach also enables a programmer to change a building block and requalify it without needing to requalify all other building blocks. Using IaC templates to provision infrastructure components and implementing these templates as building blocks ensures consistency.

AUTOMATION

By using automation, a programmer can set up IT infrastructure environments and components more rapidly in a standardized and repeatable manner. With IaC, the same tooling used for continuous integration/continuous deployment of application code can now be used to automate the deployment of IT infrastructure.

The use of automation is critical to realizing the full benefits of the cloud. Manual processes are error prone, unreliable, and inadequate to support an agile business. Frequently, an organization may tie up highly skilled staff to provide manual configuration when time could be better spent supporting other, more critical, and higher-value activities within the business.

Modern operating environments commonly rely on full automation to release software, configure machines, patch operating systems, troubleshoot, and fix bugs to eliminate manual intervention or restrict access to production environments. Automation provides the ability to make rapid changes, improve productivity, repeat configurations, reproduce environments, leverage elasticity, leverage automatic scaling, and automate testing. Many levels of automation practices can be used together to provide a higher-level end-to-end automated process.

Regulators want to see that regulated companies have control over their applications and the environment within which they run. Automation is a good way to demonstrate such control. The regulated company needs to demonstrate evidence that the automated deployment of IaC is performed according to the specification.

In Appendix D5 of *GAMP® 5 Second Edition*, Table 25.1 outlines how to demonstrate evidence that the automated deployment of IaC is performed according to specification from a risk-based approach in respect to key activities in the life cycle approach and how these principles might be applied to the testing of IT infrastructure as well [1].

INSTALLATION TESTING OF IT INFRASTRUCTURE

Organizations are usually familiar with how to perform installation testing on premise, but may be unsure how to do so in the cloud. Creating and executing a verification plan has traditionally been a manual, labor-intensive process, and it produced a static snapshot of the environment. That same process works in the cloud, too; but with IaC, it is now possible to automate the process.

With cloud technology, the whole purpose of the service responsible for deploying resources is the consistent and

repeatable deployment of the resources exactly as described in the input template. This service can be tested and verified to demonstrate that it always provides the resources as requested. Therefore, as long as the input template is controlled and approved, the confidence that the resources are deployed as expected is high and the need for verification of the output reduced, resulting in the viability of a review-by-exception approach that can replace many of the static verification activities.

Let's look at how this might work in practice. First, let's consider the "approved specification." The IT infrastructure is specified with an IaC template. This template describes the required resources and their configuration and should be deployed by continuous deployment pipelines. These templates are controlled in a similar way as source code. Storing them in a source code repository enables a programmer to version the template and keep a complete history of its evolution over time.

Another key part of the previously mentioned phrase is "approved." There are many ways to handle the approval. For example, programmers can use a Jira workflow or a pull request approval in the source code repository. Whichever method is used will be vetted and acknowledged by the IT quality and/or compliance team in accordance with a quality management system (QMS). The net result is a specific version of the template in the source code repository being recorded as approved.

The result is an approved specification describing the resources to be deployed. Once approved, the automated pipeline is triggered to deploy the resources, which will require the programmer to look at the next requirement, which is to demonstrate the installation was correct. The service that takes the template as input and performs the deployment will go through its own qualification as defined in the regulated company's QMS.

This qualification will show that deployed resources are always consistent with the template provided. Therefore, performing additional testing and reporting to confirm this after every deployment adds unnecessary time and overhead and should only be done in case of an exception. Any automation should continuously be monitored to ensure it is operating as expected and that action is taken should there be a problem.

MONITORING AND ALERTING

When creating IaC templates, it is also important to define controls that will help maintain the compliant state of resources once deployed, i.e., configuration changes that would negatively impact a security or compliance posture should be detected, alerted, and remediated.

Although any change to the IT infrastructure should go through the previously mentioned controlled automation, there is still a risk of changes happening by mistake or through malicious intent. It is therefore important to monitor the configuration of the IT infrastructure. This was problematic to accomplish with physical infrastructure but easy with IaC.

Monitoring services exist that will detect any change and trigger an assessment. Should the change violate any defined controls, an alert can be raised immediately to trigger remediation. In addition, automated remediation may be possible to revert the configuration change and even revoke the permissions of the individual that made the change.

CONCLUSION

As the name implies, IaC is code, but it is code for IT infrastructure management and hence is considered to be category 1 (IT infrastructure) for the regulated company according to *GAMP® 5 Second Edition* [1]. When leveraging IaC to create and configure infrastructure that supports specific business requirements, the regulated company should nonetheless assess (following a risk-based approach) the suitability of the provisioned infrastructure for its intended use.

The cloud service providers are expected to follow good engineering practice and are thus expected to specify, verify, and keep their services in continuous control because these are used as building blocks by the regulated companies. This is supported by supplier assessments, quality agreements, and service level agreements where appropriate, with associated suppliers supported by recommendations in section D9 of *GAMP® 5 Second Edition* [1]. To fully realize the benefits of IaC, it should be used together with automation, leading to increased quality in both compliance and operational stability. However, general principles for the use of IaC, as well as definitions of responsibilities, should be defined within organizations.

References

1. International Society for Pharmaceutical Engineering. *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)*. North Bethesda, MD: International Society for Pharmaceutical Engineering, 2022.
2. National Institute of Standards and Technology. "Glossary, IAC." Accessed 3 October 2023. https://csrc.nist.gov/glossary/term/iac
3. European Medicines Agency. Committee for Medicinal Products for Human Use. "Concept Paper on the Revision of Annex 11 of the Guidelines on Good Manufacturing Practice for Medicinal Products – Computerised Systems." Published 19 September 2022. www.ema.europa.eu/en/documents/regulatory-procedural-guideline/concept-paper-revision-annex-11-guidelines-good-manufacturing-practice-medicinal-products_en.pdf
4. Europe Commission Public Health. "EudraLex-Volume 4 – Good Manufacturing Practice (GMP) guidelines." https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

About the authors

Anders Vidstrup is a Senior IT Quality subject matter expert at NNIT, working with quality aspects of computer-related systems. Anders is responsible for deliverables to pharmaceutical and financial customers. For the past 23 years, he has been involved in the qualification of process control systems in a large plant for drug production, lab systems, and administrative GxP systems, including the full stack from infrastructure to application, for both on-premises and cloud solutions. Anders represents the Danish Standards organization, part of the International Organization for Standardization, on health informatics standards and artificial intelligence. He has been a contributing writer for several GAMP® Good Practice Guides and is Chair of the Cloud Community of Practice and a member of the GAMP® Europe Community of Practice Steering Committee. Anders has a background as a mechanical engineer and a graduate diploma in business administration. He joined ISPE in 2000.

Anette Westphal is an IT Quality Specialist at Novo Nordisk specifically supporting IT infrastructure and cloud-based implementations. She has over 20 years of experience within this area covering the roles technical operation specialist, compliance consultant, IT auditor and her latest, IT quality specialist. She joined ISPE in 2020.

Leveraging *GAMP® 5 Second Edition* FOR MEDICAL DEVICES

By Ralph Dröge and Peter Schober, PhD

This article provides a brief introduction into the standards and regulations for medical devices. It compares the *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* [1] and applicable ISPE GAMP Good Practice Guides against the relevant regulations and standards for the development of software for medical devices and demonstrates *GAMP® 5 Second Edition's* applicability.

The standards discussed in this article are 21 CFR Part 820 [2] and ISO 13485:2016 [3] for the quality management system, IEC 62304 [4] and IEC 82304-1 [5] for the software development life cycle, and ISO 14971 [6] for the application of risk management to medical device software.

The standards for the design and development of medical devices and *GAMP® 5* have different focuses. To provide the necessary understanding, the design process for medical devices, the risk management process applied to medical devices, and the software development process for medical device software are first introduced, and the system life cycle is applied to the GxP-critical systems of *GAMP® 5 Second Edition* for comparison.

Opportunities for leveraging *GAMP® 5 Second Edition* for medical devices and vice versa are also identified in this article. Steps for optimization will be proposed and can be applied in scenarios where the advantages of *GAMP® 5 Second Edition* are leading, e.g., inclusion of an IT system used as the backend of a complex medical device, or for inclusion of a mobile device managed according to the *GAMP® Good Practice Guide: A Risk-Based Approach to Regulated Mobile Applications* [7].

VALIDATION OF SUPPORTING SOFTWARE AND COMPUTERIZED SYSTEMS

As in pharmaceutical manufacturing, where computerized systems "used as part of a GMP regulated activities" [8] must be validated, quality management systems for medical devices require validation of systems used in production, quality management, or service provision.

This list can also include systems that are used in the design and development of medical devices, as demonstration of conformity of the designed product includes a demonstration that the systems, instruments, and software used to support product design and development are fit for their intended use. This is comparable to pharmaceutical industries, where *GAMP® 5 Second Edition* is not only applied to systems used in manufacturing processes, but also to systems in preclinical research and drug development.

Although it was originally created for the pharmaceutical industry, *GAMP® 5 Second Edition* may be applied for systems supporting the life cycle of a medical device. Usage of *GAMP® 5 Second Edition* for this purpose is widely practiced and accepted in medical device industries.

The first edition of *GAMP® 5* excluded "software embedded within medical devices" [9], but the scope of *GAMP® 5 Second Edition* now explicitly includes "Medical Device Regulations (where applicable and appropriate, e.g., for systems used as part of production or the quality system, and for some examples of Software as a Medical Device [SaMD])" [1].

This broadening of the *GAMP® 5 Second Edition* scope was also already anticipated by the publication of *GAMP® Good Practice Guide: A Risk-Based Approach to Regulated Mobile Applications* in 2014 [7]. With a detailed comparison of the standards explained in the following sections, we can outline the steps to harmonize a company's software and IT activities.

Figure 1: Regulations and standards for medical devices.

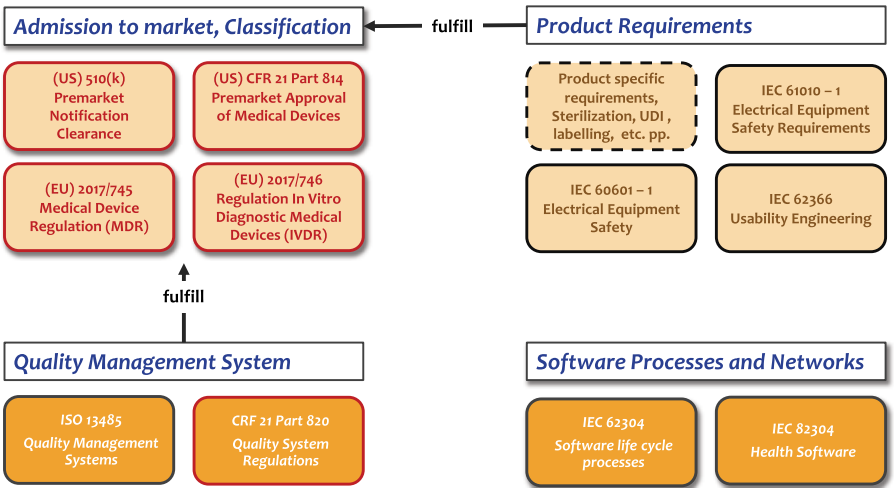
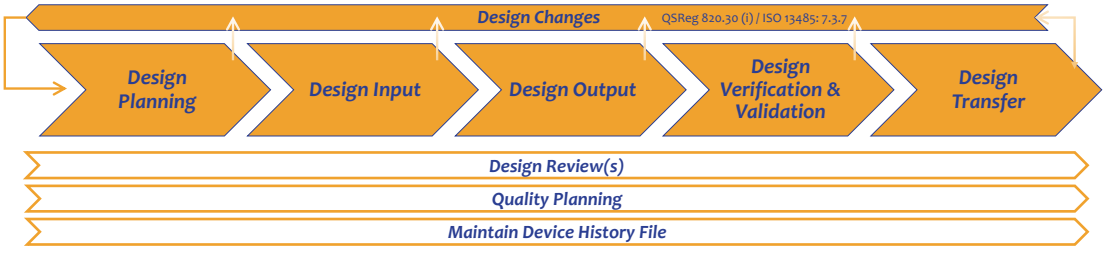


Figure 2: Medical device design life cycle based on CFR and ISO.



Alternatively, ISO/TR 80002-2 [10] may be applied for validation of systems supporting the medical device life cycle. This is not a harmonized standard, but rather a technical report that acts as a guideline like *GAMP® 5 Second Edition*. In terms of content, it is very close to the US AAMI TIR36 [11], published in 2007, which is a Recognized Consensus Standard used as a methodological basis by the FDA for the medical device industry.

MEDICAL DEVICES: STANDARDS AND REGULATIONS

Medical devices are devices used according to the intention of the manufacturer for the diagnosis, treatment, or monitoring of patients. To minimize risk for the patient, medical devices are controlled by regulations and standards.

Regulations and standards include general regulations for authorization of medical devices to the market, implementation of a quality and risk management system, medical device product standards, and more. If the medical device includes software, process standards for development and maintenance of software are also included (see Figure 1).

UNDERSTANDING LIFE CYCLES

It is essential to realize that *GAMP® 5 Second Edition* and the medical devices standards deal with different objects and processes. Consequently, a simple ad hoc mapping of activities, artifacts, and documents must be avoided. On the other hand, both *GAMP® 5 Second Edition* and the medical devices standards must manage and control software development and implementation. It is necessary to compare the different regulatory landscapes to understand how each approach to software development and maintenance disciplines varies.

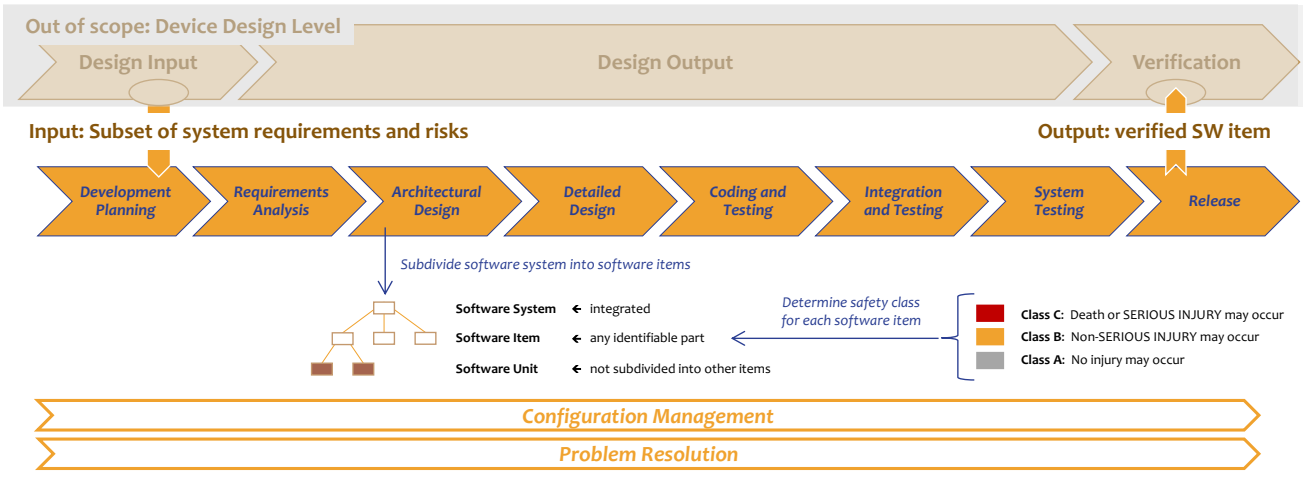
The following discussion displays for each examined medical device process the controlled objects and scope of the life cycle progression, providing a structured approach for comparison with validation life-cycle of *GAMP® 5 Second Edition*, where the controlled object is the computerized system, and the scope of the life cycle extends from the initial concept through implementation and operation to retirement or replacement of the system.

Design Control for a Medical Device

The quality management system for medical devices, according to ISO 13485:2016 [3] and 21 CFR Part 820 [2], includes the process for design control of a medical device from initial planning to transfer to production (see Figure 2).

- The controlled object in design control is the medical device as dedicated for the market according to its classification, e.g., according to Appendix IX of the EU Medical Device Regulation [12].

Figure 3: Software development life cycle based on IEC 62304.



The medical device can include mechanical, electrical, and software components.

- Software specifications are defined as part of the design input. The fully developed software package ready for installation into the medical device is part of the design output. Typically, a medical device includes software, mechanical or electrical components, and accompanying documentation.
- Design control applies if a product is intended to be a medical device and is classified respectively as a Class I, IIa, IIb, or III medical device. Manufacturing, packaging, labeling, storage, installation, and servicing of medical devices are not part of design control.
- The scope of the design control process is the design of a medical device, starting with its initial planning and classification and ending with its transfer to production. The approval of a medical device for the market is handled separately but relies on the correct application of design control.
- The correct design of a medical device is controlled by its related design history file, which covers all phases of the design control process, including verification and validation. In the case of possible design changes, the design control process is triggered again.

Software Development Life Cycle: IEC 62304

The IEC 62304 standard covers the controlled development of software components (software implementation) for medical devices from planning to release, as well as subsequent management of changes or software errors (see Figure 3) [4]. Software implementation fills the gap between design input and design output in design control.

- The controlled object in the software development life cycle is the software item, i.e., one node or component of a software system. The software items are defined in the related software architecture. If the controlled software item is the root element, the process covers the complete software system.
- The software development life cycle is not an independent life cycle. It inherits the software requirements from design input. The fully developed software package becomes part of the design output.
- The software items are assessed according to their safety classification (see safety classes as defined in IEC 62304). Each software item of the software system can be assessed separately. The safety classification is different from the classification of the final medical device.
- Scope of the software development life cycle begins with documentation planning and requirement analysis and ends with release of the integrated and tested software item for installation into the medical device. In case of changes or correction of errors, the software development life cycle is triggered again.
- The documentation of the software development according to initial documentation planning becomes part of the design history file of the medical device.

IEC 62304 Standard Processes

The IEC 62304 standard focuses on the software development process and defines the typical activities of the development life cycle such as planning, requirements analysis, design, implementation, verification and testing, and release [4]. (See the previous description of the software development life cycle.)

Overall, the standard describes process and documentation requirements for each phase of the software development life cycle and covers five processes:

1. The software development life cycle process
2. The software maintenance process
3. The software risk management process (includes a reference to ISO 14971)
4. The software configuration management process
5. The software troubleshooting process

Figure 4: Health software product life cycle based on IEC 82304.

The IEC 62304 standard does not stipulate a specific process model for the software development life cycle (like waterfall, V model, agile, or scrum). Instead, it contains requirements for specific activities and development disciplines and its documentation [4]. These activities represent minimum requirements for contemporary software development.

A relatively large section of IEC 62304 standard is dedicated to maintenance and troubleshooting processes. Medical device software issues are still a major driver in device recalls.

The IEC 62304 standard is based on the international standard for software life cycle processes, ISO/IEC 12207 [13], so it should not be difficult to harmonize with the *GAMP® 5 Second Edition* approach for software documentation and to use common life cycle templates to cover both fields.

The IEC 62304 software risk management process requires that criticality is always evaluated, i.e., the extent to which the software could be the cause of a hazardous situation for the patient [4]. This evaluation must be documented in the risk management cycles.

Risk control measures derived from the evaluation must be implemented, verified, and documented in such a way that full traceability between hazard and product requirements that mitigate the hazard is kept throughout the full product life cycle. In this sense, a risk in scope of the risk management is also always a design risk. Other risks, e.g., project risks, are managed separately. These risks are not in the scope of the IEC 62304 or ISO 14791 standards.

Safety Classes as Defined in IEC 62304

To minimize the effort and expense involved in documentation, the IEC 62304 standard defines so-called safety classes (see Figure 3) from Class A to Class C, reflecting increasing severity of possible harm to the patient [4]. The higher the safety class, the more completely the aforementioned specifications of the standard must be implemented. For example, IEC 62304 requires only the software specifications and software approval for Class A software items; even testing is not required except testing of the fully integrated system [4].

The safety classes must not be confused with the medical device classification previously described, e.g., Class I, IIa, IIb, and III, based on the level of control necessary to assure safety and effectiveness, ranging from low to high risk. The medical device classification is applied to the product, whereas safety classes are applied to one clearly identified software component: the software item (see Figure 3).

It is the responsibility of the manufacturer to establish the definition and granularity of the software system and to document it in the software architecture.

The standard uses three terms to describe the breakdown of a "software system" defined as the fully integrated software. The software system can be a subsystem of the medical device or a stand-alone medical device.

A software system consists of one or more software components, called "software items," and each software item may also consist of one or more software items. "Software units" are software items that cannot be further broken down. It is the responsibility of the manufacturer to establish the definition and granularity of the software system and to document it in the software architecture.

As previously discussed, the standard is applied not only to the integrated software system but to each software item with assigned safety class, i.e., each software item must be able to successfully pass the software development life cycle process. This introduces a high level of segregation and control of dependencies between software items.

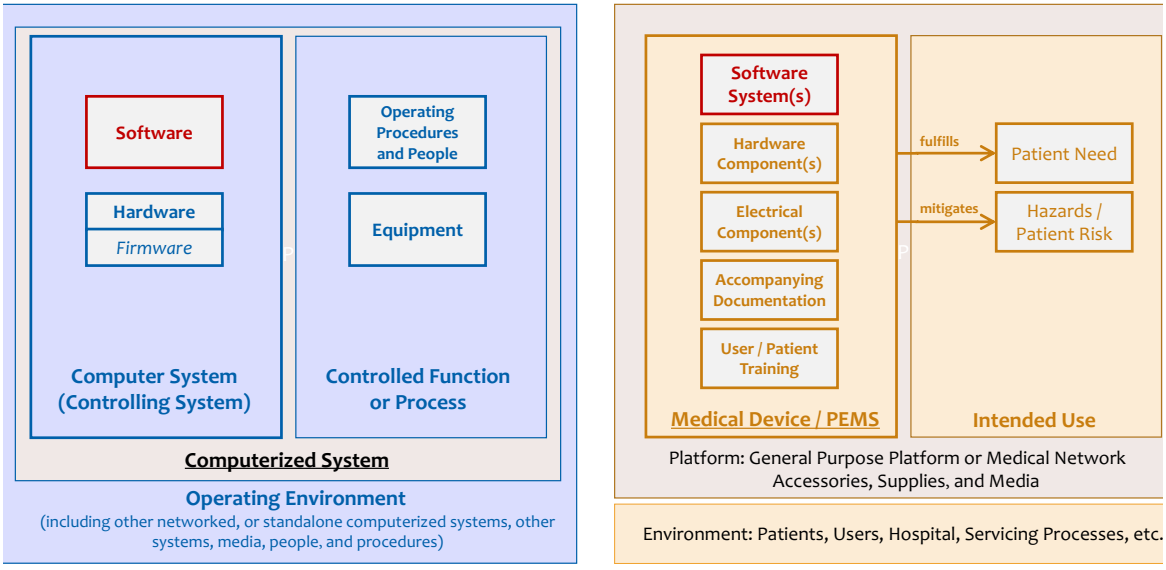
Typically, if software items that do not have a parent-child relation must interact, the software architecture will define an internal interface. Segregation of software items is a safeguard to ensure that high-risk software items are not accidentally impacted by lower risk software items.

Probability or detectability play no role in determination of the safety class; it deals only with consequences with respect to the patient. Also, data integrity and product quality, known as criteria for risk determination for GxP-critical systems, only play a role if they have consequences for the patient.

Health Software Product Life Cycle: IEC 82304

The IEC 82304 standard extends the software development life cycle previously described as applied to a software-only product (see Figure 4) [5]. It is an interpretation of the design control

Figure 5: Conceptual comparison of (A) a well-known PIC/S model of a computerized system as used in *GAMP® 5 Second Edition* and (B) a medical device, including software (a programmable electrical medical system [PEMS]).



A medical device intended to fulfill a specific medical purpose can be considered conceptually equivalent to a computer system intended to control a specific function or process.

process for software as medical device and a completion of the development life cycle for health software products that are not classified as medical devices. The following description focuses on medical devices.

- The controlled object is a health software product, which may include SaMD or other health software not classified as medical device. In the case of a medical device this means it is a fully stand-alone SaMD. Respectively, the health software product life cycle complies with the design control process for medical devices.
- For software implementation, the health software development life cycle relies on the software development life cycle according to IEC 62304 [4].
- If the health software product is intended as a medical device, it must be classified according to the medical device regulations.
- The scope of the health software development life cycle for the case of medical devices is the design control, starting with initial risk assessment and establishment of product requirements up to validation of the software product as basis for its release to market as medical device.
- The correct development of the software product for a medical device is controlled by the design history file. Contributions according to IEC 82304 [5] are the software requirements and the final validation report. In case of possible design changes, the process is triggered again.

COMPUTERIZED SYSTEM VS. MEDICAL DEVICE

For further understanding, the controlled objects treated in the life cycle models are compared based on the Pharmaceutical Inspection Co-operation Scheme (PIC/S) model for computerized systems in regulated GxP environments [22] (see Figure 5).

A medical device intended to fulfill a specific medical purpose can be considered conceptually equivalent to a computer system intended to control a specific function or process. The patient risk of the intended use of a medical device plays the same role as the GxP criticality according to an initial risk assessment for a computerized system.

Software is a key component in a computerized system, as well as in a PEMS. A medical device may consist only of software components (SaMD) that are installed on a general-purpose platform, like a mobile device, or are deployed with a medical network.

COMBINING IEC 62304 AND IEC 82304

Requirements for software are only a subpart of the requirements for a PEMS:

Figure 6: V Model of a PEMS in accordance with IEC 82304.

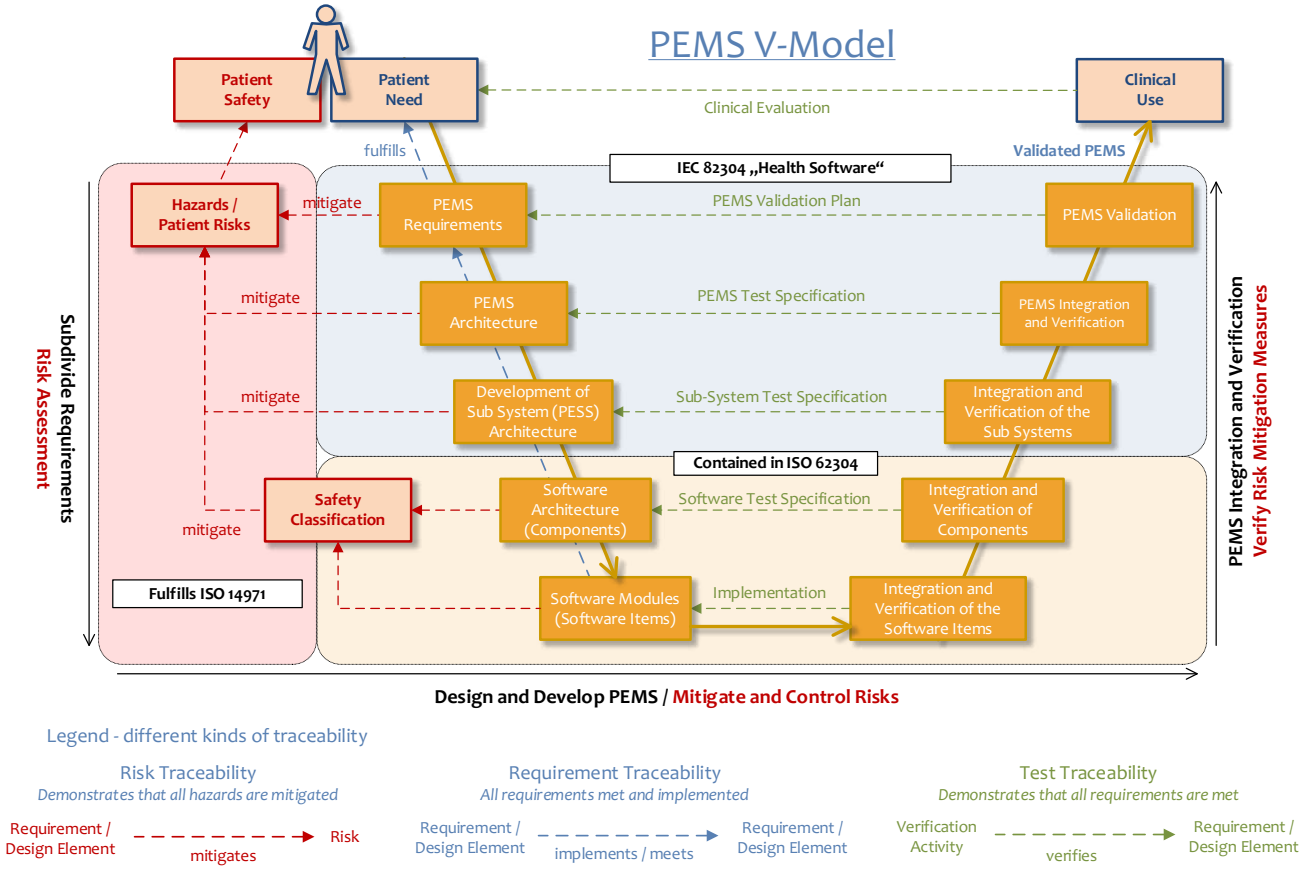


Figure 6 shows a schematic diagram of a V model of PEMS development. The specifications of IEC 62304 apply only to the PEMS component level and below. Validation is defined as the "evaluation of whether a product meets the requirements for the intended purpose" [14] and the "confirmation [...] that the requirements for a specific intended use or a specific intended application have been met" [3].

That is, validation requires a clearly defined intended use and valid requirements for use. As IEC 62304 focuses particularly on software items embedded in medical devices, requirements for software verification are formulated, but not for validation. Therefore, medical device manufacturers can rely on the standard IEC 82304 ("Health Software"), which covers the top section of the V model in Figure 6 and is also applicable to stand-alone software, or SaMD [5].

CONCLUSION

We have shown that *GAMP® 5 Second Edition* can be fully compatible with medical device needs when a few points or gaps are correctly understood and appropriately addressed. Bringing the worlds of GxP-critical IT systems and medical device software together requires limited initial effort.

As soon as these steps have been taken, the advantages of GAMP (e.g., in system operation, management of critical data, early quality involvement, and leveraging of supplier activities) are revealed for the medical device world. The GAMP world can take advantage, in particular, of medical devices teams' expertise on software architecture and segregation, management of design risks, and software development.

An in-depth comparison of the medical device processes with *GAMP® 5 Second Edition* including a roadmap for harmonization will be given in an upcoming ISPE/GAMP concept paper.

References

1. International Society for Pharmaceutical Engineering. *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)*. North Bethesda, MD: International Society for Pharmaceutical Engineering, 2022.
2. US Food and Drug Administration. 21 CFR 820: Food and Drug, Medical Devices, Quality System Regulation. 4 February 2020. www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-820
3. ISO Standard 13485:2016. "Medical Devices, Quality Management Systems, Requirements for Regulatory Purposes, Third Edition." March 2016. www.iso.org/standard/59752.html

4. IEC Standard 62304: 2006/Amid 1:2015. "Medical Device Software, Software Life-Cycle Processes." June 2015. www.iso.org/standard/64686.html
5. IEC Standard 82304-1:2016. "Health Software – Part 1: General Requirements for Product Safety." October 2016. www.iso.org/standard/59543.html
6. ISO Standard 14971:2019. "Medical Devices, Application of Risk Management to Medical Devices, Third Edition." December 2019. www.iso.org/standard/72704.html
7. International Society for Pharmaceutical Engineering. *ISPE GAMP® Good Practice Guide: A Risk-Based Approach to Regulated Mobile Applications.* North Bethesda, MD: International Society for Pharmaceutical Engineering, 2014.
8. European Commission. "EudraLex, Volume 4: EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use. Annex 11: Computerised Systems." Published 2011. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/annex11_01-2011_en.pdf
9. International Society for Pharmaceutical Engineering. *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems.* North Bethesda, MD: International Society for Pharmaceutical Engineering, 2008.
10. ISO/TR Standard 80002-2:2017. "Medical Device Software — Part 2: Validation of Software for Medical Device Quality Systems." June 2017. www.iso.org/standard/60044.html
11. Association for the Advancement of Medical Instrumentation. "AAMI TIR 36: 2007: Validation of Software for Regulated Processes." Technical Information Report. Published 2008. https://webstore.ansi.org/preview-pages/AAMI/preview_AAMI+TIR36-2007.pdf
12. European Union Medical Device Regulation (MDR) 2017/745. "Appendix IX—Conformity Assessment Based on a Quality Management System and on Assessment of Technical Documentation." www.medical-device-regulation.eu/2019/08/14/annex-ix/
13. ISO/IEC Standard 12207:2017. "Systems and Software Engineering, Software Life Cycle Processes." November 2017. www.iso.org/standard/63712.html
14. IEC Standard 60601-1-11:2015. "Medical electrical equipment — Part 1-11: General Requirements for Basic Safety and Essential Performance, Collateral Standard: Requirements for Medical Electrical Equipment and Medical Electrical Systems Used in the Home Healthcare Environment." January 2015. www.iso.org/standard/65529.html

Acknowledgments

The authors would like to thank the members of the Germany/Austria/Switzerland (D/A/CH) Affiliate Application of GAMP 5 in the Medical Device Field special interest group (SIG) for their continuous support and contributions.

About the authors

Ralph Dröge is an independent consultant for quality management, project management, and compliance. His customers include well-known companies from the life sciences sector. In his 25 years of experience, he has managed numerous IT projects for the pharmaceutical and medical device industries, especially in the areas of manufacturing execution systems, laboratory information management, enterprise resource planning, and life cycle management for software and products. He is founder and Chair of Germany/Austria/Switzerland (D/A/CH) Affiliate Application of GAMP 5 in the Medical Device Field special interest group (SIG). He holds a degree in astrophysics and has been an ISPE member since 2009.

Peter Schober, PhD, works as Principal Consultant at gempex. He has more than 25 years of experience from projects in research, pharmaceutical industry, medical technology, and in-vitro diagnostics in quality assurance, IT, and GxP environments. As a consultant, he supports his clients in application development, system integration in international rollouts, IT supplier auditing, organizational projects, and validation of computerized systems for new implementations and optimization projects. Peter is a certified auditor for Medical Device Software, a speaker at conferences, and an author. He holds a PhD in chemistry from the University of Heidelberg.

Pharmaceutical Engineering® Announces the 2022 Article of the Year

Pharmaceutical Engineering® magazine is proud to announce that the 2022 Roger F. Sherwood Article of the Year is "Supporting Cell and Gene Therapy through Multimodal and Flexible Facilities" (November/December 2022) by Stephen Judd and William G. Whitford.

The article focuses on the unique needs and considerations for cell and gene therapy (C&GT) manufacturing suites and how they differ from those for classic product biopharmaceuticals.

"The article wins the 2022 Article of the Year award because the authors describe the processes and supply challenges, the GMP's requirements, and the biosafety precautions that major companies, contract development and manufacturing organizations (CDMOs), and start-ups should consider before building multipurpose, flexible manufacturing facilities to produce successful new allogeneic and autologous treatment platforms. The article is very useful for each C&GT professional and stakeholder in development and manufacturing," said Ferdinando E. Aspesi, Senior Partner, Bridge Associates International, and Chair of the Pharmaceutical Engineering Committee (PEC).

ABOUT THE AWARD

ISPE's Roger F. Sherwood Article of the Year award was established in 1993. Three decades later, the award showcases the best content in *Pharmaceutical Engineering*®, increases industry recognition, highlights ISPE's reputation as a global knowledge leader, and bolsters magazine content quality.

Although various judges have taken part in assessing articles over the years, one constant remains: recognition of quality and excellence in content by identifying finalists and a single winning article for each publication year.

2022 JUDGING

A subcommittee of the PEC served as judges for the 2022 award competition, reviewing articles and providing assessments on the following criteria: usefulness to ISPE readers; how the articles improve the knowledge of key topics; and clarity and ease of reading.

2022 AWARD FINALISTS

The other articles selected as finalists for the 2022 Roger F. Sherwood Article of the Year were:

- "Measuring Pharma's Adoption of Industry 4.0" (January/February 2022)
  By Toni Manzano and Agustí Canals, PhD
- "Driving Biopharma Solutions with Digital Technologies" (January/February 2022)
  By Martin Mayer
- "A Governance and QA Framework: AI Governance Process Design" (July/August 2022)
  By Elias Altrabsheh, Martin Heitmann, FRM, and Albert Lochbronner
- "Integrating Knowledge Management and Quality Risk Management" (July/August 2022)
  By Martin J. Lipa, PhD, Valerie Mulholland, and Anne Greene, PhD
- "Introduction to Steam Quality and Testing" (July/August 2022)
  By Nissan Cohen, Nicholas Haycocks, Jeremy Miller, FIET, FinstR, Derek Mullins, and Keith Shuttleworth

CHARLIE WAKEHAM

An ISPE member since 1999, Charlie Wakeham has been active within the ISPE GAMP® com-munity since 2001. A founding member of the GAMP UK Community of Practice (CoP), she is currently Chair of the GAMP Global CoP Steering Committee, one of the leaders of the GAMP Computer Software Assurance Special Interest Group (SIG), and a member of the ISPE Guidance Documents Committee. She has co-led or contributed to nine published ISPE GAMP guides and was co-lead of the Data Integrity SIG. She was also a member of several planning committees for ISPE conferences, including the 2023 ISPE Annual Meeting and Expo.

Charlie's career in the pharmaceutical industry began when she was working on her postgraduate project for her Master of Science. "It was supposed to be a six-month project building a filter sterilization system for an injectable drug. It was interesting, and I was learning a lot, and I enjoyed being involved with something that was providing a benefit to the community. I ended up staying on with the company for 18 years in a variety of roles."

After moving to Australia in 2013, Charlie began working for Waters Corporation. As their Asia-Pacific (APAC) GxP Compliance Manager, she set up a professional services group delivering computerized system validation (CSV) and data integrity consultancy. Her validation of Waters' Empower Chromatography Data System and NuGenesis Lab Management System for customers in Australia, New Zealand, China, Korea, and Southeast Asia brought her a deep understanding of the APAC region's challenges and opportunities.

After a short spell as Global Head of Quality and Compliance at Magentus (formerly Citadel Health), Charlie is now operating as an independent consultant. Her company, WakeUp to Quality, specializes in resolving quality and compliance challenges for GxP organizations. Her practical experience in quality management systems, CSV, and data integrity is combined with her extensive GAMP knowledge to deliver pragmatic solutions using critical thinking and patient-centric approaches.

"I have always been passionate about making a difference, making things better. I now have the opportunity to bring that to a broader range of companies. My focus is always to understand the customer's internal processes and intended use and to deliver a solution that is correspondingly fit for purpose, whether it's a simple standard operating procedure or a complex validation project."

Charlie says she hears from professionals on a regular basis who tell her GAMP® has helped them with their career. "I co-led, with Lorrie Vuolo-Schussler, the production of three GAMP Records and Data Integrity Good Practice Guides—they were published in 2018, 2019, and 2020, and recently I had someone reach out on LinkedIn saying how much these guides help them in their work. It means so much to me that in such a complex and critical area, something we did is still helping people."

One of Charlie's goals as Chair of the GAMP Global CoP Steering Committee is to encourage early- and mid-career professionals to get involved. "My advice to emerging leaders is to volunteer, get involved, say yes to every opportunity that presents itself. Don't worry if you don't have a clear vision of your career plan. Sooner or later, you'll find your niche and grow. ISPE has had a tremendous positive impact on my career, and it can do the same for you, if you invest the time and energy to be active in the organization."

Additionally, Charlie is setting up the Steering Committee for GAMP South Asia for ISPE members in Australia, Indonesia, Malaysia, Philippines, Singapore, Thailand, and New Zealand. In 2019, Charlie was recognized with the ISPE Max Seales Yonker Member of the Year Award for her volunteer work with GAMP and for the training she has provided to regulatory agencies.

—Marcy Sanford, ISPE Publications Coordinator

LORRIE VUOLO-SCHUESSLER

Lorrie Vuolo-Schuessler has been involved with ISPE and GAMP® projects since 2002. She has authored or co-led 11 ISPE GAMP-focused guidance documents, including *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* and the *ISPE GAMP® Good Practice Guide: Enabling Innovation - Critical Thinking, Agile, IT Service Management*. She is Immediate Past Chair of the GAMP Americas Steering Committee, a member of the GAMP Global Leadership team, and a co-leader of the Computer Software Assurance (CSA) Special Interest Group (SIG). Additionally, she has contributed to multiple ISPE and GAMP webinars, expert exchanges, conference presentations, and trainings.

Early on, Lorrie knew she wanted to work in the pharmaceutical industry, but her path to a career in quality assurance and computer systems compliance started with an interest in chemistry. "I had an older cousin I really looked up to who studied chemistry and then worked in the pharmaceutical industry. Where I grew up in north New Jersey, there were a lot of pharmaceutical companies, and I wanted to follow in her footsteps," said Lorrie. "My first job after college was working at the America Health Foundation, a cancer research center where they were doing cutting edge research on nutritional chemistry."

From there, Lorrie worked at Revlon and Ciba-Geigy before joining GSK, where she started as a scientist studying drug metabolism before moving into safety assessment and quality assurance and computer systems compliance.

"This was at the time when Good Laboratory Practice was being introduced into drug metabolism labs and GAMP was being introduced in the US," Lorrie said. "And I started working with other ISPE members on the laboratory SIG, and eventually co-lead the team which wrote the first edition of the *ISPE GAMP® Good Practice Guide: A Risk-Based Approach to GxP Compliant Laboratory Computerized Systems.*"

Throughout her career, Lorrie has been instrumental in ensuring that the best quality systems are in place and GAMP has helped support that. "GAMP is focused on quality, critical thinking, and risk-based approaches. Instead of creating reams of useless information, it focuses on the quality elements of the project, not just checking boxes."

"I think that is where the pharmaceutical industry needs to go. That's what the CSA draft FDA guidance is doing, really trying to get people to focus on the quality of what they're doing and not the perceived regulatory compliance aspect of it. Because if you build quality into your processes and into your product, it will be compliant. But if you are only looking at the compliant aspects, you may miss quality. It is really important to focus on the quality aspects of what we do and not just what we perceive to be a compliance cause."

In addition to helping shape her career, Lorrie's involvement with GAMP has given her a group of lifelong friends. She says the main advice she gives to any young person is to get involved. "I look at the people I'm involved with in GAMP and think I am surrounded by amazingly intelligent, brilliant people, who have done so much and brought so much into the industry, and I feel honored to be among them. I've traveled with them, worked on guidance with them, and what we've done has influenced the industry in a positive way."

Last year at the 2023 ISPE Annual Meeting & Expo in Las Vegas, Nevada, Lorrie was honored with ISPE's Richard B. Purdy Distinguished Achievement Award. Named after one of the Society's founders and most accomplished presidents, the award honors an ISPE member who has made significant, long-term contributions to the Society.

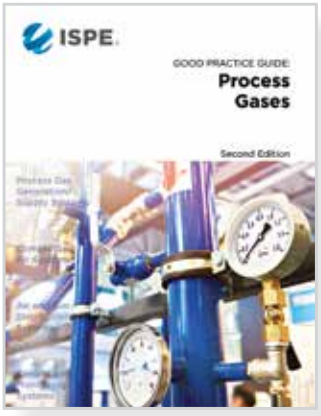
—Marcy Sanford, ISPE Publications Coordinator

New Good Practice Guide Covers Pharmaceutical Gas Systems

The new *ISPE Good Practice Guide: Process Gases, Second Edition* presents recent advances in construction materials and updates on current good practices. It was revised based on the latest International Organization for Standardization in Pharmaceuticals, American Society for Testing and Materials, and American Society of Mechanical Engineers standards and is aligned with the latest regulatory guidance.

"This guide provides comprehensive information about process gases," said Guide Co-Lead Stephan Neumann, Global Governance, Critical Utilities, Boehringer Ingelheim GmbH. "It covers all aspects of pharmaceutical gas systems, including generation technologies and design options for control/monitoring and system operation, and sustainability requirements. It also presents general properties and characteristics of the atmospheric gases and compressed air, along with pharmacopeia requirements."

This second edition adopts the *ISPE Baseline® Guide: Commissioning and Qualification (Second Edition)* integrated commissioning and qualification strategy to streamline the effort for process gas systems. System designers are encouraged to consider where the gas will be used and for what purpose when developing the user requirements for use points.



"This is the best guidance in the industry for process gases," said guide Co-Lead Nissan Cohen, Owner, Biopharmaceutical Water Doc. "There are annexes of the guide illustrating examples for sampling strategies for oral solid dosage, active pharmaceutical ingredients, and sterile fill and finish plants using risk assessment methodologies, process analytical technology principles, and modern manufacturing systems. This document is the only comprehensive process gas guideline in the entire biopharmaceutical industry."

To learn more about this and other ISPE guides, visit ISPE.org/publications/guidance-documents

Meet the ISPE STAFF

Nina Wang

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Nina Wang, Editor-in-Chief, *Pharmaceutical Engineering®*.

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

Before stepping into my new role as Editor-in-Chief, I served as a technical editor for guidance documents here at ISPE. While my primary responsibility was content review and refinement, my daily routine encompassed a wide range of tasks throughout the guide development process—from getting authoring teams off the ground and running and coordinating schedules all the way to the final proofread just before publication.

What do you love about your job?

The people! One of the most rewarding aspects of working at ISPE is the opportunity to collaborate with our global network of volunteers. We have the privilege of uniting individuals from around the world, each contributing their expertise and a genuine passion for sharing their knowledge. I would be remiss if I did not also mention the dedicated and hardworking team of ISPE staff.

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

On the weekends, you'll often find me on the sidelines of a soccer field, cheering on my kids and their teams. We also enjoy discovering new places to eat or immersing ourselves in the beauty of the redwoods, as well as planning our next vacation!

2023 ISPE **Annual Meeting & Expo**

Attendees Hit the Educational/Networking Jackpot at Annual Meeting

Over 2,800 attendees from across 27 countries and 200 exhibitors gathered in Las Vegas, Nevada, in mid-October for the 2023 ISPE Annual Meeting & Expo. The conference kicked off with workshops and the Emerging Leaders Hackathon, where 17 teams competed to answer Roche/Genentech's request for consultation on how to make single-use technology more sustainable through the key perspectives of supply chain manufacturing and automation.

After the 5K run and walk on Monday morning, attendees heard from keynote speakers, discussing patient perspective, new ways of delivering drugs, and the role the pharmaceutical industry should play in combatting climate change.

Sustainability was the overarching theme bridging the educational tracks which included digital transformation, manufacturing, quality control, operational excellence, supply chain resiliency, Advanced Therapy Medicinal Products, and regulatory compliance and quality. Twenty-five technical concurrent sessions were held over two days. Other conference highlights included the Member Luncheon, an interview with US Food and Drug Administration (FDA) Commissioner Dr. Robert M. Califf, and the Women In Pharma® self-defense class.

Attendees had the opportunity to network at special events such as the Sunday Social, Women In Pharma's Allure of the Ally, the Expo Hall Welcome Reception, and the Member Appreciation Party at the Mob Museum. Other celebrations included the President's Reception, the Volunteer Recognition Event, and the Facility of the Year Awards Celebratory Reception & Banquet.

The conference concluded with a global regulatory town hall and a closing ceremony in the Expo Hall followed by a golf tournament supporting the ISPE Foundation the next day.

Make plans now to join us in Orlando, Florida, for the 2024 Annual Meeting & Expo. For more information, visit ispe.org/am24

Global Regulatory Town Hall: David Churchward (Lonza), Paul Gustafson (PIC/S and Health Canada), Dr. Celia Lourenco (Health Canada), Dr. Vimal Sachdeva (WHO), and Mahesh Ramanadhan (FDA)

2023 ISPE Annual Meeting & Expo

Snapshots and Attendee Insights

"The patient advocate, Matthew Pearl's presentation resonated with my passion for the pharmaceutical industry."

"The education sessions and workshops provided insightful and engaging discussions."

President's Reception

5K Run/Walk

"I had the opportunity to meet vendors and end-users, addressing needs and services in the market."

"I made great connections and networking opportunities from all activities."

Facility of the Year Award Celebratory Banquet

Women in Pharma®

ISPE Hosts a Fireside Chat with FDA Commissioner

By Randolph Fillmore

In a prerecorded interview shown during a keynote session at the 2023 ISPE Annual Meeting & Expo, Tom Hartman, ISPE President and CEO, and Dr. Robert M. Califf discussed several far-ranging and important topics. Califf, the US Food and Drug Administration (FDA) 25th Commissioner is a recognized expert in cardiovascular medicine, health outcomes research, health care quality, and clinical research with a long, distinguished career as a physician, researcher, and leader in science and medicine.

Before joining the FDA for the second time, Califf was the Head of Medical Strategy and a senior advisor at Alphabet, Inc. Prior to his time at Alphabet, Inc. he served as a professor of medicine and as Vice Chancellor for clinical and translational research at Duke University. He was also the founding Director of the Duke University Clinical Research Institute.

In the interview, Hartman and Califf discussed the harmonization of pharmaceutical and biologic innovation and manufacturing, improving patient access to drugs for rare diseases and the current global regulatory efforts to achieve this, emerging technologies such as artificial intelligence (AI), FDA and industry cooperation during the COVID-19 pandemic, preventing drug shortages, and maintaining the quality of the industry and regulatory workforce.

Hartman: The regulatory harmonization of innovation and manufacturing and the analysis of pharmaceuticals and biologics are critical for meeting the needs of patients now and in the future. The FDA has been a true leader in these areas for a number of years by providing industry with mechanisms to discuss and implement innovation and emerging technologies.

If our industry is to successfully leverage this innovation to positively impact global supply resiliency and patient access, we believe steps are necessary for regulatory alignment and convergence. What can the FDA do to facilitate interactions with health authority peers, such as the Quality Innovation Expert Group in the European Medicines Agency (EMA), the World Health Organization Innovation Hub, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, or similar groups?

Califf: This is an important issue. If we don't innovate in the manufacturing of drugs, we're really letting the world down. I was thinking about this during my recent trip to India. There are 1.4 billion people in India. In the US, we tend to think about the Indian generic industry as something that serves the US, but there is a much larger population to be served. There are 7.6 billion people who live outside the US, so we have a lot to do to make manufacturing resilient and to have it serve the needs of so many people. To do that, we have to interact with our fellow regulators. As you are aware, we are harmonizing guidances now with our recent "Q13 Continuous Manufacturing of Drug Substance and Drug Products" guidance coming out.

While working together is important, I don't think we want total convergence because a lot of what leads to innovation is the ability for smaller units to step up rather than regress to the lowest common denominator of what we all have in common. I think a key part of the US approach is going to be to continue to try to be leaders in innovation, but where there is an establishing technology—as it evolves—we should work with our collaborators around the world.

Hartman: Global patient access to medicines and therapeutic products for rare and ultra rare diseases poses a significant challenge for both industry and regulatory authorities. Is there an opportunity here for leading regulators—such as the FDA, EMA, and others—to develop a globally agreed upon approach for clinical and commercial development and approval of these novel and life-altering therapies?

Califf: We should be able to work together to identify everyone with a rare disease, no matter where they live. And using our aggregate

intelligence and technology should make it possible for them to get a diagnosis and to enter clinical trials. There is a cluster that has been formed that involves EMA, FDA, and Health Canada.

We are meeting together and talking, but, as I pointed out in the last question, India has 1.4 billion people, China has 1.5 billion people, and the Association of Southeast Asian Nations and the sub-Indian and sub-Chinese part of Asia add another 1.5 billion people.

So, we have a large portion of the world's population that we're not communicating with. That has to be an important part of our strategy as we work together on guidances and accelerating rare disease cures programs. There are differences in resources around the world, of course, and we can't act as if that's not the case, so it's really important—I think—for the US to lead the way.

Hartman: I think that's a very good perspective, as the industry is constantly evolving and placing significant emphasis on emerging technologies that facilitate faster access to medicines for patients globally. One area of high interest is "model informed drug development," or MID.

With MID, physiological-based models can improve clinical trial efficiency, optimize drug dosing, and potentially reduce the number of patients in a trial, or even decrease the number of clinical studies to support the approval of a particular medicine. Can you share your thoughts on the potentially beneficial impacts of this program for patients, and do you see an opportunity to extend or even accelerate this initiative for global consideration?

Califf: Early in my career, we worked on predicting outcomes for people with coronary disease, and I learned pretty quickly that if you just depend on raw data, without modeling, you leave out a lot of knowledge that can be gained by looking at how the data fits together.

Today we're in a new era that is extraordinarily exciting. Call it AI. Call it machine learning. But we can now take diverse data sources, with different types of data, and that enables us to create models that include disparate kinds of data. That creates the ability to do things that just couldn't be done before.

I am pretty excited about using AI to identify targets, then look at the configuration of proteins and molecules in a way that enables us to not only more quickly identify what the real candidates are, but also to use the models to predict where the toxicities might be. I think this might really make a difference.

Hartman: To shift gears around some of the learnings from the pandemic, given the FDA's leading role in working with industry to expedite development and approval of vaccines, how is the FDA leveraging that experience and translating it to address unmet medical needs and even approval accelerations, particularly with respect to therapeutic and technical innovations domestically as well as globally?

Califf: I don't like using the term "accelerated approval." That term may imply that we always approve, but 85% of drugs that get introduced into phase one trials don't make it. So, it's really "accelerated evaluation," and the approval is based on biomarkers, which is another place where modeling is a very important part of the overall effort. We have multiple ways that we can accelerate, depending on the particular circumstance, such as a priority review where we want to make a decision within six months.

Today we're in a new era that is extraordinarily exciting. Call it AI. Call it machine learning. But we can now take diverse data sources, with different types of data, and that enables us to create models that include disparate kinds of data. That creates the ability to do things that just couldn't be done before.

I do want to point out one more thing. In the haste to say that we have learned about doing everything fast, as if it's just a matter of having less bureaucracy, we should not forget the COVID-19 vaccine effort. That effort was, I believe, perhaps one of the most momentous scientific achievements in history, given the speed at which that vaccine was developed and how effective it has been.

The government put in a lot of money, and we shouldn't lose sight of the fact that it's not just how fast we go through the regulatory review. It's about the resources put into the scientific concepts and the articulation of industry, academia, and government—all working toward the same goal.

I don't want to disappoint people who may hope that we are saying, "now we can go twice as fast, and it's no problem." I think the answer to this is mixed. We should go faster where we can but still have confidence that we're not opening the field up to ineffective or dangerous treatments.

Hartman: That's an excellent point. Now to shift to drug shortages. On the part of both industry associations and regulators, there have been recent efforts to mitigate drug shortages. As you may know, ISPE has recently issued its Drug Shortages Prevention Model, and I know that the FDA has focused on preventing drug shortages. And, we have seen some legislation in support of enhanced reporting and transparency.

Does the FDA feel the current reporting expectations have been effective to predict and even mitigate shortages? And what other measures can the FDA and industry implement in partnership to reduce shortages significantly and sustainably?

I think AI is going to be a companion to everything we do. Whether it's a drug, a biologic, or a device. AI should reduce the amount of cutting and pasting that goes on to free up our brains to work on the creative part and the human part—that's really needed.

Califf: When demand goes up, there is a potential for an impending shortage. You can predict that almost any inexpensive generic drug is at risk of shortage. We can produce probabilities, but what really produces a shortage is when a line goes out in a manufacturing plant, or there's some problem, like in Ukraine, where there is a shortage of raw material. We need a system that's resilient to those factors.

So, having said all that, we want to make the best predictions we can, but we need to be able to plug the holes when they occur. But, right now, we've got 200–300 impending shortages every year, and it will continue that way until we fix the economics of the industry.

Hartman: And in that regard, there has been a lot of conversation around reshoring manufacturing. Do you feel that the US or other countries have an overreliance on foreign or geographically concentrated sources for either manufacturing the material, the drug, or key starting materials that ultimately result in shortages?

Califf: I do think there's overreliance. The whole world needs access to generic drugs, so what we need is a balanced geographic distribution. The key starting materials, the raw materials, are far over-concentrated in China. So, I was really pleased when I saw that India is making a good faith effort to do environmentally sound starting-material transformations into active pharmaceutical ingredients. I'm gaining a lot of confidence that we can get a geographic balance. We just have to decide to do it.

We've taken this amazing gift of very inexpensive, highly effective drugs, generics, and created a contracting system that guarantees that there will be shortages. So, we have to fix the contracting so that the companies that make generic drugs have adequate security, so that they can attract investors to keep their technology and equipment updated, so that they can manufacture high-quality products with enough in the supply chain to have a reserve on hand. You can predict that almost any inexpensive generic drug is at risk of shortage if one or two bad things happen.

Hartman: From the FDA's perspective, what are the big, enduring lessons learned from the pandemic and what is the FDA currently planning, implementing, or preparing for the next pandemic? Also, how can industry and the FDA have a partnership in preparation for the next pandemic?

Califf: As I mentioned before, I think one of the big lessons learned is that when we all agree on a problem, we decide we're going to go all out to fix it, and the government pumps money into the system, we can accomplish miracles.

A second lesson was the investment in platform development that happened with mRNA over the course of 15–20 years. We need to keep working together on platforms so that we can be ready to deliver when the need occurs. We also learned a good bit about the steps and where you can take a calculated risk in terms of FDA review. If you have a situation where people are dying, and there's no effective treatment, well that's different. We know the calculated risk that we can take.

I also would mention the dedication and resilience of the FDA workforce. I was on the outside when this all started. I came in in the middle of it, and it was amazing to see how strong people really were, considering all the night and weekend work that had to be done. I think that's just an attribute of all the elements involved—FDA, industry, and, of course, academia going night and day.

Hartman: From your perspective, what topics could be best leveraged by AI? Or, what activities could be leveraged by AI in terms of medicines development, manufacturing, or, ultimately, product licensure?

Califf: I think AI is going to be a companion to everything we do. Whether it's a drug, a biologic, or a device. AI should reduce the amount of cutting and pasting that goes on to free up our brains to work on the creative part and the human part—that's really needed. I think generative AI could also open a window into something that can be terribly biased and lead to really bad results. Or it can free us up from bias, depending on how we use it.

What should the guardrails be on the use of AI, particularly as it becomes more generative across all these things? How do we police it? How do we turn it in the right direction? I know an evolutionary biologist who says, "There is no invisible hand of justice in an AI algorithm." So, we must keep that in mind. It's important not just for us, as regulators, but for industry to look at AI very carefully and highlight the need for a robust control framework to keep AI within the guardrails.

Hartman: You spoke earlier regarding the Center for Biologics Evaluation and Research hiring a number of individuals. One of the industry's challenges, which I think has been exacerbated post-pandemic, is the availability of a capable workforce to fill critical medicines development manufacturing and related roles.

Many companies have established internal programs where they look to organizations like ISPE to implement programs similar to our student travel grant program that enlists students to participate in conferences and gets them introduced to the industry. Does the FDA have similar challenges in this space and, if yes, how are you addressing workforce issues?

Califf: We are constantly worried about the workforce, especially in scientific areas. There must be a constant infusion of new people who are recently trained at the cutting edge or have been out in industry working at the cutting edge. We have to compete for those people, but we also need to grow them, so we have an extensive program for students of all types, from high schools and colleges to postdocs. There are over 1,000 students, and about half of those students come back and begin working at the FDA.

We also have something called the ORISE Fellowship. It is run out of the Department of Energy, and we're one of the major users of that program, particularly for postdocs who can come in and work at the FDA. I feel like we play our role in developing the workforce of the future, some of which stays at the FDA. Many go into the industry with a knowledge and appreciation for the regulatory side—something that academia traditionally doesn't teach very well.

Hartman: Yes, it's a big issue and we also are trying to address it as part of ISPE's remit. Now, with the fourth quarter of 2023 upon us, a lot of organizations—and I'm sure the FDA as well—are preparing their budgets and activities for 2024. What are the big challenges and what do you see as the leading priorities for the FDA as we head into 2024?

Califf: We're facing a very tough financial situation in 2024. The budget—at best—is flat. I would say our number one challenge is just surviving the financial situation that we're going to be in and, of course, dealing with the Congress and the election year, particularly one that's so dramatically frustrating as this one, where people just aren't working together. That's a challenge.

On the other hand, I've never seen an explosion of biotechnology like we have now. I think the medical products side of the FDA is doing great, and it will continue to be able to respond to what's needed. The biggest emphasis for me is the food side of the FDA, where we're doing a complete reorganization of the human foods program. Biotechnology applied to agriculture is, I think, going to turn out to be one of the most important things. We must have resilient plants and animals and production of protein independently of polluting the atmosphere. And that's dependent on smart regulation to help the industry get to where it needs to go.

Randolph Fillmore is the director of Florida Science Communications, Inc. He has written on health care and health care policy, medical research, pharmaceutical and medical device regulation, public health, biology, chemistry, physics, pharmacy, and the social sciences. Formerly, he was employed as a science writer at the Johns Hopkins University School of Public Health and later at the University of Maryland Baltimore School of Pharmacy. He has been a member of the National Association of Science Writers since 1994. He has a BS in Anthropology, an MA in Medical Anthropology, and an MA in Journalism.

ISPE Announces the 2023–2024 Board and Honor Award Winners

By Marcy Sanford

As part of the 2023 ISPE Annual Meeting & Expo, the 2023–2024 ISPE International Board of Directors was introduced and the gavel was passed to a new Chair on 16 October 2023 during the 2023 ISPE Membership Meeting and Awards Lunch in Las Vegas, Nevada.

CHANGES TO THE BOARD

Incoming Chair Scott W. Billman, Vice President of Engineering for Pharmaceutical Services at Thermo Fisher Scientific, began his year as Chair. Outgoing Chair Michael L. Rutherford, Executive Director of Computer Systems Quality and Data Integrity at Syneos Health, moves into the Past Chair position of the International Board's officers.

The Membership Meeting included presentations by Rutherford, Billman, and Thomas Hartman, ISPE President and CEO, as well as reports on the financial health of ISPE and an update on the ISPE Foundation.

Sharing that ISPE was in a strong position for growth, Rutherford gave an overview of ISPE's accomplishments in 2023, which include a new website that allows members to more easily access their benefits, increased engagement with emerging leaders, the formation of a new student grant program, the implementation of the 2023–2025 Strategic Plan, and continued execution of One ISPE.

ISPE Board of Directors Immediate Past Chair Michael L. Rutherford (right) passes the gavel to incoming Chair Scott W. Billman.

Liz M. Dooley, Zen-Zen Yen, Hirofumi Suzuki, Norman A. Goldschmidt, Michael Martin, David Churchward, Jeffrey A. Biskup, Ylva Ek, Scott W. Billman, Teresa Minero, Jörg Zimmermann, Vivianne J. Arencibia, Michael L. Rutherford, Georg Singewald, and Thomas B. Hartman

"ISPE membership has increased nearly 30% from mid-2020. ISPE now has more than 21,000 members in over 120 countries."

"The goal of One ISPE is to make sure that we are connecting with all the affiliates and chapters. In 2023 we added our 40th chapter—the Southwest Chapter, who are hosting this event." Rutherford also thanked outgoing board members Jörg Zimmermann, Vice President of Vetter Development Service and External Affairs at Vetter Pharma-Fertigung GmbH & Co. KG, and Zen-Zen Yen, Head of Engineering at Bayer AG, for their contributions as they step off the board.

Hartman welcomed attendees to the Membership Meeting and spoke about the ways ISPE members are helping shape the future of the pharmaceutical industry: "All of our accomplishments are thanks to you."

"ISPE membership has increased nearly 30% from mid-2020. ISPE now has more than 21,000 members in over 120 countries and our goal is to have 25,000 by 2025. This year we increased the number of Communities of Practice (CoPs) from 19 to 22 and we have plans to create an additional three, focusing on artificial intelligence, sustainability, and pharma compounding."

"We have increased the number of guidance documents we publish. Conference attendance is increasing in numbers when compared to pre-pandemic levels. We have a very active, productive, and industry-relevant regulatory steering council. It is all thanks to you, our subject matter experts. You are the lifeblood of ISPE," said Hartman.

Billman introduced the 2023–2024 board and presented ISPE's goals for 2024. "Looking ahead, we want to engage more students and emerging leaders, expand our global reach through engagement and inclusion, continue to drive technical innovation through CoPs, and continue to have more interaction with global regulatory experts. We are committed to continue to evolve and grow ISPE, deliver value to our members, and celebrate the successes of our industry."

THE 2023–2024 INTERNATIONAL BOARD OF DIRECTORS

Officers

Scott W. Billman
Chair
Vice President, Engineering, Pharmaceutical Services
Thermo Fisher Scientific

Jeffrey A. Biskup, PE
Vice Chair
Executive Board
Chairman/Co-Founder
CRB

Vivianne J. Arencibia
Treasurer
Vice President, Global Quality Systems and Compliance
Moderna

Ylva Ek
Secretary
Founder
Robur Life Science Advisory AB

Michael L. Rutherford
Immediate Past Chair
Retired, Computer Systems Quality & Data Integrity

Thomas B. Hartman
Ex Officio Non-voting Member
President and CEO
ISPE

Directors

Nina S. Cauchon, PhD
Director, Regulatory Affairs, CMC
Amgen Inc.

David Churchward
Global Head, Sterility Assurance, Cell and Gene Technologies
Lonza Biologics

Liz M. Dooley, MSc
Senior Director, Global Engineering and Technology
Johnson & Johnson

Norman A. Goldschmidt
President
Genesis AEC

Michael Martin
CEO
CAI

Sarah C. Pope Miksinski, PhD
Executive Director, CMC Regulatory Affairs
Gilead Sciences, Inc.

Teresa Minero
Founder and CEO
LifeBee - Digitalizing Life Sciences

Georg Singewald, PhD
SVP, Global Head of Engineering, Technology and Sustainability
Roche/Genentech

Hirofumi Suzuki, PhD
Product Supply Japan, Head of Product Supply Coordination
Bayer Yakuhin Ltd.

Timothy J.N. Watson, PhD
Vice President, Head of CMC Regulatory Affairs
Gilead Sciences

Ex Officio

Emerging Leaders Representative (non-voting)
Monique L. Sprueill, PMP
Director, GCP Quality Lead
Bristol Myers Squibb

2023 INTERNATIONAL HONOR AWARDS

The 2023 ISPE Honor Awards were distributed to recipients by Hartman, Rutherford, and Billman.

2022 ISPE Roger F. Sherwood Article of the Year Award

"Supporting Cell and Gene Therapy through Multimodal and Flexible Facilities" (November/December 2022)

Authors

- Stephen Judd, Arcadis DPS Group
- William G. Whitford, DPS Group (pictured)

2023 ISPE International Emerging Leader Hackathon Winning Team

Hack O' Lantern

Team members

- Alma Navarro Carmona, Operations Rotation Development Program Analyst II from Genentech
- Christian Harper, Regional Sales from Stilmas Americas
- Saurav Jain, chemical engineering student from North Carolina State University
- Evangeline Colarossi Keiss, Formulation Scientist II from Tolmar Inc.
- Isabella Tobin, pharmacy student from Purdue University
- Anna Sun, Process Simulation Engineer from CRB
- Filipp Voronov, QC Chemistry I from Fujifilm Diosynth Biotech

2023 Company of the Year Award

Roche

2023 ISPE Affiliate and Chapter Excellence Award

Ireland Affiliate

2023 ISPE Committee of the Year

Advancing Pharmaceutical Quality (APQ) Initiative Team

2023 ISPE Max Seales Yonker Member of the Year Award

Diane L. Hustead
Executive Director, Regulatory Affairs
Merck & Co Inc.

2023 ISPE Richard B. Purdy Distinguished Achievement Award

Lorrie L. Vuolo-Schuessler
GAMP Americas Steering Committee
Retired, GSK and Syneos Health

2023 ISPE Joseph X. Phillips Professional Achievement Award

Frances M. Zipp
President and CEO
Lachman Consultant Services

2023 ISPE Facility of the Year Award

Genentech South San Francisco Clinical Supply Center

ISPE Announces the 2023 Facility of the Year Award Winner

At the 2023 Facility of the Year Award (FOYA) Celebratory Banquet, ISPE announced the 2023 overall FOYA winner: Genentech's Clinical Supply Center (CSC). In addition to winning the overall award, Genentech's CSC project was recognized as the 2023 Pharma 4.0™ category winner for its bold objectives, innovation, and deep team alignment and integration.

ABOUT THE FACILITY

The evolution of clinical therapies and the advancement of artificial intelligence, automation, single-use technologies, and digitization have updated the requirements for optimal operation of pharmaceutical manufacturing facilities. For the Genentech team, the CSC was an opportunity to do something bold and create a facility that could deliver on the promise of medical innovation while ushering in a new era of manufacturing for the biotech company.

The CSC was completed in November 2022 after 19 months of development. Located in South San Francisco, California, it is a 78,000-square-foot, 2,000-liter-scale, small-volume clinical biologics facility. During design, every opportunity to push the envelope was evaluated, including the facility layout, equipment choices, digitization tools, and team organization. The resulting facility is surprisingly simple and dynamic in its design.

The facility touts a ballroom layout, or open floor plan, eliminating the need for separate rooms and teams. This change from the standard facility design allowed for a product-agnostic layout with downstream flexibility. Because of these design choices, the facility can quickly adapt to producing different therapies while simplifying utility lines and reducing the need for specific equipment.

The design—which includes fully integrated automation, robotics, and operations management systems—also enables a central team to run the facility. Paired with fully digital validation and paperless manufacturing operation, the CSC is built for agility and speed while maintaining high-quality standards for the safety of patients.

Planning for the future went beyond integrating the latest and greatest technologies. Sustainability was an objective the team kept front of mind, beginning with a life cycle assessment of the facility and continuing throughout the facility's construction. The CSC, now LEED Gold certified, generated renewable energy, significantly reduced energy and water use, and made extensive efforts to minimize waste.

Built to be a template for future Genentech facilities, the CSC mixes technical and operational innovations with a straightforward, strategic approach to facility design. The cutting-edge facility delivers improved outcomes in terms of construction, safety, sustainability, facility productivity, and improved patient access to innovative medicines.

ABOUT ISPE'S FOYA

Since 2005, ISPE's FOYA has recognized state-of-the-art projects using new, innovative technologies to improve the quality of products, reduce the cost of producing high-quality medicines, and demonstrate advances in project delivery.

Each year, submissions are accepted from projects worldwide, representing breakthroughs in various disciplines, from automation and integration to the development of medicines for underserved populations. Ultimately, a panel of industry leaders chooses the projects that set the standard to receive FOYA in the following categories:

- Innovation
- Operations
- Supply Chain
- Pharma 4.0™
- Social Impact

To learn more, visit ISPE.org/facility-year-awards

Golf Tournament Supports ISPE Foundation

By Tori Johnson

On 19 October, the ISPE Foundation hosted its 2nd Annual Golf Tournament at Wildhorse Golf Course following this year's Annual Meeting & Expo in Las Vegas.

The tournament, filled with friendly competition and casual networking amongst Nevada's mountains, was more than just golf—it was about making a difference.

The Foundation supports access to ISPE's many resources while making strides toward improving workforce diversity throughout the pharmaceutical industry. Proceeds from the tournament benefited the Greatest Needs philanthropic pillar and supports the Foundation's mission of fueling global health equity by fostering access to knowledge and nurturing diverse talent.

We are immensely thankful for this year's sponsors whose support allows us to continue to better our industry; which in turn makes a difference for patients around the world. We eagerly look forward to next year's Annual Golf Tournament in Orlando, Florida. To learn more about 2024 sponsorship opportunities, contact Isabella Stoup, Development Coordinator (istoup@ispe.org) or Tori Johnson, Director of Development and Foundation Operations (tjohnson@ispe.org).


ISPE Foundation
2ND Annual Golf Tournament Sponsors
GOLF


GENESIS


GOLF
PREMIUM HOLE SPONSOR
Boston
ANALYTICAL
ISPE


PROJECT FARMA
A PRECISION FOR MEDICINE COMPANY


The Moirae
GROUP, LLC
WWW.THEMOIRAEG.COM

CALIBRATION PERFORMANCE IMPROVEMENT CASE STUDY

By Pitoyo Amrih and Pringgo Widyo Laksono, DrEng, ST, MEng

Calibration plays a critical role in ensuring a measurement instrument's accuracy—especially if the instrument has a direct impact on product quality and patient safety. However, the calibration process is a complex system, and the traditional analytical approach for planning this process is often not sufficient to improve service performance. Using a digital simulation model as a representation of the actual situation allows creation of optimization scenarios for improvement purposes before they are implemented.

The pharmaceutical industry is highly regulated. Within its jurisdiction, each country has an authorized agency that closely supervises industry operations to protect the users of their products. Each country's regulatory agencies have the obligation and authority to protect the drug's consumer by safeguarding the quality of the final products, assessing the production process and all facilities involved (buildings, instruments, machines, equipment, and utilities), and controlling the raw material used [1].

Instrument calibration is one of the regulation requirements that ensures the fulfillment of product quality and patient safety. Regulations expressly state that the pharmaceutical industry must carry out calibration activities for measurement instruments to ensure the quality of the products produced, the safety of the personnel involved in the manufacture of the product, the safety of medicinal product users, and the safety and sustainability of the environment [2].

CALIBRATION

Calibration ensures the accuracy of a measuring instrument throughout its traceable chain. The pharmaceutical industry must follow strict guidelines to calibrate each critical measuring instrument and ensure the quality of medicinal products produced as part of Good Manufacturing Practices (GMP) implementation [2].

However, companies must also be competitive, carrying out organizational activities effectively and efficiently so that they can produce affordable medicinal products for patients. A smooth-running supply chain of industrial activities is important, not only for core activities (raw materials, production processes, finished goods, and distribution networks), but also for all supporting departments within the internal organization [3]. Studies for bottleneck identification and process optimization in other industries have been carried over to the pharmaceutical industry for support functions, such as the quality control laboratory [4], that can provide regular quality inspection services for raw materials, work in process, and finished goods and balance them as to not disturb production processes.

In order to meet quality and technical requirements, a pharmaceutical company that also implements the calibration laboratory for internal support functions must also develop resources for calibration activities according to its respective provisions. Technical requirements include various resources that must be prepared, including highly trained personnel and their capabilities, calibration environment, equipment, and calibration methods. The high-level skills of calibration personnel and the existence of written detailed methods for each calibration activity are the keys to effective calibration services [5].

The pharmaceutical industry has a range of measuring instruments of various types [5–7]. For example, temperature-measuring instruments can range from simple portable glass thermometers to delicate thermo controllers located in complex sterilization systems. Each equipment item may require the development of its own unique method, although all methods must still refer to the concept of temperature calibration standards [8–10]. Likewise, the development of calibration methods for other types of measuring instruments commonly used in the pharmaceutical industry must use necessary calibration method references, such as weight and balance calibration [11–13], pressure gauge calibration [14–16], and various other types of instrument calibration where the methods is developed specifically by the manufacturer of the instrument. This means calibration activities are varied.

Processing calibration data is used to issue a calibration accuracy certificate that also serves as a legal document. This data must also include the calibration uncertainty that can create complex systems for managing the thousands of instruments in a large factory area coverage [17]. However, science and technology developments have created breakthroughs in data processing

systems and calibration administration management [18–20].

Instrument calibration in the pharmaceutical industry covers a scope that is as varied as the variety of instruments being calibrated, making a traditional mathematical analytical approach for planning insufficient. A system model approach that can mimic the real situation of the system is needed to accurately help provide an overview between calibration load and availability of resources and to make the right decision for optimization.

SIMULATION MODEL APPROACH

The simulation model approach used for the calibration laboratory area in this case study aims to act as an enlargement of the studies of simulation models that have been carried out in quality control laboratories in the pharmaceutical industry [4, 21]. Simulation is one of the most widely used operations research and management science techniques [22]. With a simulation model approach, we can study and complete experimental research for a complex system in many scenarios and observe the outcome in every simulation run to find the optimal solution for improvement [23–25].

For pharmaceutical industry cases, simulation models have helped decision-makers improve system performance in quality control laboratory cases and production line manufacturing [26–28]. Today, simulation has become a popular industry optimization tool because it can be embedded into smart factory components for building an Industry 4.0 concept as a key enabling technology for the availability of big data and the Internet of Things [29–35].

Discrete event simulation as a specific terminology of operation research's simulation model was introduced in 1950 as a scientific approach method to understand, improve, and optimize manufacturing processes in the industry. Discrete event simulation is also used as basic knowledge development of the digital twin model [36, 37].

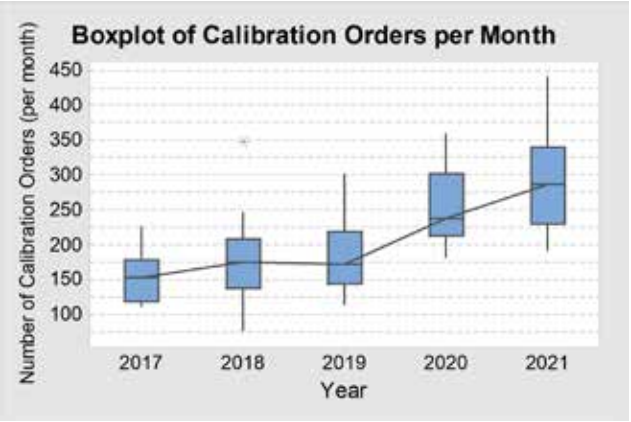
To build a simulation model of a system, a system boundary must be created at the initial stage with the necessary definitions and modeling of the simulation parameters, including location, entities, activities and delays, process logic, resources, and arrival rules [23, 25]. Currently, a lot of simulation software can be used to generate random data distributions with patterns that resemble the conditions of the system and collect the simulation result to be observed and analyzed [38–40].

This case study uses the discrete event simulation method and the simulation model is developed using ProModel 2016 software. Hypothesis testing of the developed simulation model showed no statistical difference between the simulation model and the actual situation, meaning the digital simulation model can be used as a representation of the actual situation and companies can then simulate improvement and optimization scenarios using this model.

CALIBRATION CASE STUDY

A pharmaceutical company in Indonesia with an internal calibration laboratory support function was chosen for the discrete event simulation application study. At the time the research was conducted, the company had 5,536 instruments registered as

Figure 1: Calibration order increase per month.



calibration objects with various periodic calibration intervals, instrument types, and calibration execution lead times. It was found that 97% of the instruments were calibrated by the company's internal calibration laboratory, with around 30% of the calibrations completed inside the laboratory facility, and 70% completed onsite where the instruments were installed or located.

Periodically, calibration orders will arrive on a specific date, but random calibration orders also arrive daily—for example, for initial calibration for a new instrument, when a user requests calibration before a due date, or when a user finds an out-of-tolerance situation in a daily check that urgently needs recalibration. On average, the company had about 300 calibration orders requested per month in 2021. When reviewing these numbers, it should be noted that some calibration technicians put in unplanned overtime and about 8% of orders were for instruments past their calibration due date that had to be pulled from use until the required calibration was completed. Figure 1 shows the increase in calibration orders per month from 2017 to 2021, illustrated as a boxplot to show the variation between months in one year.

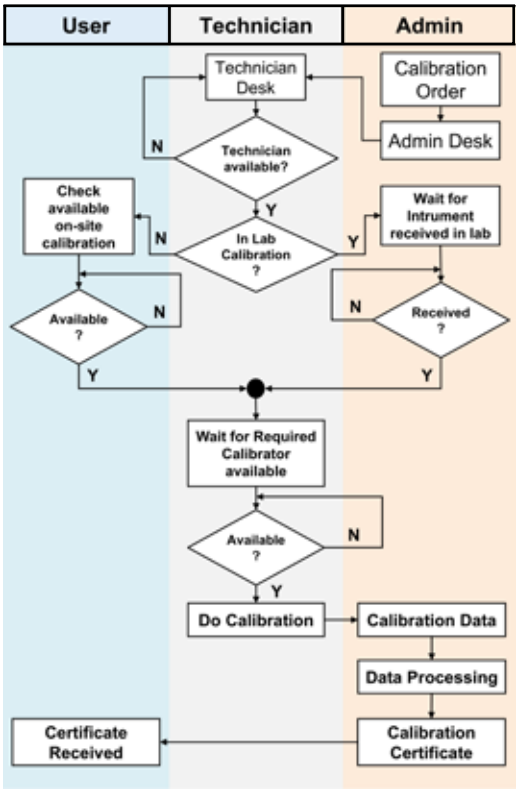
Traditional mathematical analytical approaches for trial and error experiments that use the actual system are too expensive. Further, the high degree of uncertainty and the randomness of calibration order arrivals make the study too complex for the analytical planning approach. The study used a discrete event simulation model and application software to mimic a calibration laboratory service situation. Such a model can be used to conduct experiments with the goal to determine optimized solutions for problem situations and to solve instrument calibration service performance problems.

CASE STUDY METHODOLOGY

The method used in this research consists of the following steps:

Define calibration laboratory model design. The first step was to create a system model for the company's calibration system. The system model was made according to the actual situation stages but was simplified to be easier to observe and analyze.

Figure 2: Calibration laboratory service system flowchart.



Collect data and fit statistical distribution. Data collection and statistical analysis were carried out at each stage of the calibration service process and on every step of the model. Goodness of data distribution fit test analysis was carried out; later it was used as a reference to generate random numbers in the simulation run.

Develop a discrete event simulation model. The model is developed to match the calibration laboratory service system. The simulation model is created using simulation software.

Verify the simulation model. The simulation model is verified with several samples of actual conditions to hypothesize whether there is a significant difference between the simulation model created and the actual conditions.

Study the optimal solution for calibration order demand scenario. Some scenarios to find the optimal condition are simulated assuming the estimated load of future calibration order.

LABORATORY MODEL DESIGN

A typical pharmaceutical laboratory calibration system was observed to identify the process within the system. Figure 2 shows the calibration service process steps as a flowchart. The process begins with a calibration order that, in many cases, is an automatic, scheduled command received from the management computer system to complete the required periodic calibrations at specified intervals. The order can also be generated randomly based on user needs and requirements. The calibration order is then received at the administration desk and forwarded to the technician desk. The order is tasked to a technician, who takes the order to get calibration data.

There are two groups of calibration tasks:

1. In the calibration laboratory (in lab): In the lab, there is a waiting time to send instruments from the user to the calibration laboratory, and a waiting time for calibrator availability.

2. Onsite calibration: Onsite, there is a waiting time for equipment shutdown that will allow calibration to be carried out, and waiting time for calibrator availability. This group is further divided into three groups based on the travel time required from the technician desk to locations with different building groups, which are categorized into pharmaceutical product plants (onsite pharm), herbal product plants (onsite herbs), and plant category for food supplement (onsite food).

For both task groups, technicians will have random spans of time available to carry out work for another calibration order while waiting for instrument and/or calibrator availability.

The loading time for calibration based on time measurement samples has a certain data distribution pattern. After the calibration process is complete, calibration data is brought to the administration desk by technicians, which is then processed and ratified into a calibration certificate. Calibration certificates are sent to users as soft copy and distributed electronically.

For the study, the company had more than 5,500 instruments registered as calibration objects and an average calibration order of 300 orders per month. The calibration orders appeared spread over one month; however, on certain dates there was an automatic surge in demand as periodic calibration orders for instruments with a next-month calibration date came due. At the time of the study, the company had four calibration technicians performing calibrations. From the data collection, the technicians were performing calibrations only 30%-60% of the time, because their job also required carrying out machine qualification and process validation activities.

DATA COLLECTION

The required data were collected for calibration laboratory service activities for six months, from 1 January 2021 to 30 June 2021. The data were then processed and analyzed for a goodness-of-fit test distribution. An initial sample observation was completed in month 1. The goodness-of-fit test to the data distribution of calibration order arrives every month as the data obtained fit to an exponential distribution. Data in month 2 to month 6 were also analyzed and the goodness-of-fit results showed that all arrival data fit with an exponential distribution. It could then be justified that the calibration order arrival data follow a random pattern based on an exponential distribution.

The same method was used to measure the time of delays, including waiting time for the instrument to be available for calibration (to be received in the calibration lab for in-lab calibration or for equipment shutdown for onsite calibration), waiting time for the calibrator to be available, and the calibration activity duration. All data also have to be analyzed for the goodness-of-fit test distribution. The same analysis was carried out for data collection on delays and activities at the administration desk and technician desk, up to when the calibration certificate was received by the user.

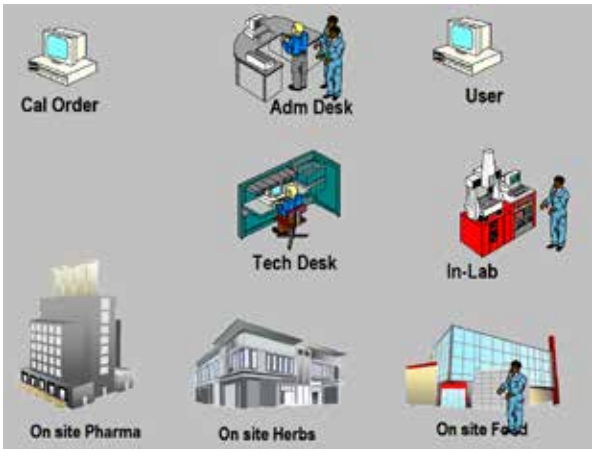
SYSTEM MODEL

The discrete event system model was created using ProModel 2016 software with a mimic model simulation, as shown in Figure 3 and with the parameters shown in Table 1.

MODEL VERIFICATION

The model was then verified using the simulation, running with arrival distribution at the time of the data collection. The results were compared with the actual data to test statistically whether there were significant differences. The tested output collection statistics were: the number of exit calibration certificates (CalCert), average time of the orders inside the system (tavg-ent), and percent of utilization of time used by technicians to perform calibration activities against normal loading time (Tech-utl) with three technicians (at month 1, 2, and 3) and four technicians (at month 4, 5, and 6) as a resource. Table 2 shows the verification result.

Figure 3: Mimic model simulation in ProModel 2016.



The test using a two-sample t-test between the simulation model and the actual shows the p value for the number of exit calibration certificates (CalCert) is 0.360, for the average time of the entities inside the system (tavg-ent) is 0.255, and percent of utilization of time used by technicians to perform calibration activities against normal loading time (Tech-utl) is 0.974. Using a significance level of 0.05 indicates that all output statistic parameters collected from model simulation have p value more than 0.05. The p value is greater than the significance level, but there is not enough evidence

Table 1: Parameter set on the model simulation built from analyzed data value.

Input			Output					
Location	Entities	Logic	Location	Entities	Logic	Probability	Operation Time	Move Time
Cal Order	CalOrd	Random	Adm Desk	CalOrd	No queuing	100%	E(0.4) min	E(2.0) min
Adm Desk	CalOrd	Random	Tech Desk	CalOrd	Random	100%	E(14.3) min	N(286.2,84.5) min
Tech Desk	CalOrd	Random	In Lab	CalOrd	Random	38%	E(0.4) min	L(3832,2534) min
Tech Desk	CalOrd	Random	Onsite Phrm	CalOrd	Random	30%	E(0.4) min	N(7726,3345) min
Tech Desk	CalOrd	Random	Onsite Herbs	CalOrd	Random	13%	E(0.4) min	W(5.5,11466) min
Tech Desk	CalOrd	Random	Onsite Food	CalOrd	Random	19%	E(0.4) min	N(5490,2503) min
In Lab	CalOrd	Random	Adm Desk	CalData	FIFO	100%	E(14) min	E(2.5) min
Onsite Pharm	CalOrd	Random	Adm Desk	CalData	FIFO	100%	E(79.9) min	E(3.1) min
Onsite Herbs	CalOrd	Random	Adm Desk	CalData	FIFO	100%	W(2.1,51.8) min	L(16.1,2.1) min
Onsite Food	CalOrd	Random	Adm Desk	CalData	FIFO	100%	W(1.2,140) min	N(20.7,2.9) min
Adm Desk	CalData	Oldest	User	CalCert	FIFO	100%	W(1.2,3.9) min	EXIT

E(a) means the data distribution fit the exponential distribution with mean a; W(a,b) fit the Weibull distribution with shape value a and scale value b; N(a,b) fit the normal distribution with mean a and standard deviation b; L(a,b) fit the lognormal distribution with mean a and standard deviation b.

Table 2: Verification result of the simulation model.

Timeline	Number of Technicians	Total Hours	Arrival Logic	CalCert		tavg-ent (min)		Tech-utl (%)	
				Model	Actual	Model	Actual	Model	Actual
Month-1	3	220	E(30.26)	261	239	9825	7516	42.50	54.17
				254		10466		50.12	
				254		9422		50.00	
Month-2	3	223	E(47.81)	215	203	8936	11737	43.07	37.44
				228		9356		43.32	
				198		8901		42.18	
Month-3	3	301	E(42.15)	304	274	9166	11742	44.01	40.26
				301		9691		42.30	
				276		9167		42.59	
Month-4	4	273	E(31.23)	331	283	10090	10381	54.14	52.12
				318		9921		53.71	
				317		10308		52.68	
Month-5	4	242	E(47.11)	204	218	8948	8711	29.88	34.26
				229		8905		33.91	
				237		8668		37.79	
Month-6	4	312	E(62.74)	226	258	9356	9130	25.59	31.78
				235		8771		27.96	
				238		9321		32.60	

E(a) means the data distribution fit with the exponential distribution with mean a.

to conclude that the difference between the simulation model and the actual situation is statistically significant.

PROPOSED IMPROVEMENT

The model was then used to create a simulation with an estimated load calibration order scenario for 2022. The 2022 scenario had an average of 350 orders per month, based on the analysis of the 2017–2021 orders and a 2022 order projection load (refer to Figure 1). The scenario used the normal number of technician hours available without overtime in one month, which is 173 hours; four technicians; and the arrival rule on the assumption of 350 orders per month, which is equivalent to an E(29.6) distribution. In this scenario, the results showed a 202 calibration certificates completed, with average time of orders within the system at 10,075 minutes and 54.29% technician utilization (this utilization is within the range that ensures time available for qualification and validation tasks). In this scenario, a large number of calibration orders were beyond past the due date (37.1%), so opportunities remain. Some improvements for optimization that can be analyzed from the simulation model run are as follows:

Completing 350 calibration orders per month followed by 350 calibration certificates per month can only be achieved if the four technicians are each scheduled for approximately 100 hours of overtime a month. The simulation model shows that adding technicians will not improve the calibration service performance.

Alternatively, a strategic initiative can be set with the objective to minimize significance delays. For example, considering at the most likely calibration situations—in-lab calibration and onsite pharmaceutical plant calibration—by reducing the delay time by 40%, the simulation shows that the system can complete 350 calibration orders and 321 calibration certificates per month. Using the simulation model, it is known the remaining orders can be accomplished with approximately 15 hours of technician overtime in one month. Another option is to increase investment so the in-lab capacity can be doubled, because this type of calibration has the highest probability of being successful. Simulation shows this strategy will allow competing 344 calibration certificates without requiring technician overtime.

CONCLUSION

This case study contributed to the current understanding of how using simulation methods to analyze calibrations laboratory services plays an important role in ensuring the accuracy of instruments used in supply chain production activities. The discrete event simulation model can be used to analyze a calibration

laboratory system that has a high variation in job and workload, even though the complexity of each job is very diverse. The simulation model built at this level of the research demonstrates that the model verification results have no evidence to indicate that the difference between the simulation model and the actual situation is statistically significant.

For improvement with the investment decision—such as increasing in-lab calibration capacity or minimizing delays by providing redundant strategies for calibration objects and calibrator types of the highest probability orders—it is necessary to complete further studies on the cost-benefit analysis by running more simulation models. These models can provide data on the possibility of added value obtained from the investment.

In the future, more in-depth exploration can be done by adding the simulation logic that has been developed to the existing calibration management software program so the big data collection from calibration order records can be simulated and provide optimized decision options in real time and become a convincing tool for a digital twin model. This approach can be further developed for the digital twins model of a system.

References

1. Rantanen, J., and J. Khinast. "The Future of Pharmaceutical Manufacturing Sciences." *Journal of Pharmaceutical Sciences* 104, no. 11 (November 2015): 3612–38.
2. Pharmaceutical Inspection Co-operation Scheme. "Guide to Good Manufacturing Practice for Medicinal Products Part I." PE 009-15. May 2021: 1–4.
3. Shah, N. "Pharmaceutical Supply Chains: Key Issues and Strategies for Optimisation." *Computers & Chemical Engineering* 28, no. 6–7 (2004): 929–41.
4. Lopes, M. R., A. Costigliola, R. M. Pinto, S. M. Vieira, and J. M. C. Sousa. "Novel Governance Model for Planning in Pharmaceutical Quality Control Laboratories." *IFAC–PapersOnLine* 51, no. 11 (2018): 484–9.
5. Yuvamoto, P. D., R. K. S. Fermam, and E. S. Nascimento. "Metrology in Pharmaceutical Industry–A Case Study." *Journal of Physics: Conference Series* 733, no. 1 (2016): 012041.
6. Nogueira, R. "Metrological Traceability of Measurement Results in Pharmaceutical and Chemical Sciences: Selection and Use of Certified Reference Materials." *Journal of the Brazilian Chemical Society* 26, no. 2 (2015): 209–17.
7. Fritsch, K. "Metrology of Weighing in the Pharmaceutical Industry." *Measurement: Sensors*. 18 (2021): 100262.
8. Bentley, R. E. *Handbook of Temperature Measurement*, 245, 1998.
9. National Institute of Standards and Technology. "A Procedure for the Effective Recalibration of Liquid-in-Glass Thermometer." NIST Special Publication 819. Gaithersburg. US Department of Commerce. August, 1991.
10. Vaughn, C., and G. Strouse. "The NIST Industrial Thermometer Calibration Laboratory, International Symposium on Temperature and Thermal Measurements in Industry and Science." 2001. https://tsapps.nist.gov/publication/get_pdf.cfm?pub_id=830734
11. The International Organization of Legal Metrology. "OIML R 111-1. Weights of Classes E1, E2, F1, F2, M1, M1–2, M2, M2–3 and M3. 2004;2004:80. https://www.oiml.org/en/files/pdf_r/r111-1-e04.pdf
12. The International Organization of Legal Metrology. "OIML R76-1. Non-Automatic Weighing Instruments." 2009;2009:1–62.

13. US Pharmacopeia. USP38NF33. General Chapters <1251> Weighing on an Analytical Balance. Usp38Nf33. 2015:1253–7.
14. Peggs, G. N. "A Review of the Fundamental Methods for Measuring Gauge Pressures up to 1 kPa." *Journal of Physics. E, Scientific Instruments* 13, no. 12 (1980): 1254–62.
15. Hasegawa, T., and K. Matsukawa. "Measurement of Small Pressure Difference." *Transactions of the Japan Society of Mechanical Engineers B* 57, no. 541 (1991): 3013–7.
16. The American Society of Mechanical Engineers. Pressure Gauges and Gauge Attachments. ASME B40.100, 132. ASME, 2013.
17. International Organization for Standardization. ISO/IEC. Uncertainty of Measurement–Guide to the Expression of Uncertainty in Measurement (GUM:1995). ISO/IEC Guide 98-3:2008. 2004.
18. Mehta, B. R., and Y. J. Reddy. "Industrial Process Automation Systems." 507–22. Ind Process Autom Syst, 2015.
19. Brown, C., T. Elo, K. Hovhannisyan, D. Hutzschenreuter, P. Kuosmanen, O. Maennel, et al. Infrastructure for Digital Calibration Certificates. 2020 IEEE International Workshop on Metrology for Industry 4.0 & IoT 2020: 485–9.
20. Tanaro, L. F., H. V. Pacheco, A. C. D. S. G. dos Santos, L. A. F. Ferreira, and G. N. Santos. "Lean and Metrology: A Systematic Review and Bibliometric Analysis of the Scientific Literature from the last 20 Years." *Independent Journal of Management & Production* 11, no. 5 (2020): 1576.
21. Costigliola, A., F. A. P. Ataíde, S. M. Vieira, and J. M. C. Sousa. "Simulation Model of a Quality Control Laboratory in Pharmaceutical Industry." *IFAC-PapersOnLine* 50, no. 1 (2017): 9014–9.
22. Law, A. M. *Simulation Modeling and Analysis*. Fifth Ed. New York: McGraw-Hill Education: 2013.
23. Banks, J. Introduction to Simulation. In: 2000 Winter Simulation Conference Proceedings (Cat No00CH37165). 2000. p. 9–16 vol.1.
24. Banks, J. II B. L. Nelson, and D. M. Nicol. *Discrete-Event System Simulation*. Pearson Prentice Hall, 2014.
25. Ingalls, R. G. "Introduction to Simulation." In *Proceedings Winter Simulation Conference*. 2011. 1374–88. https://doi.org/10.1109/WSC.2011.6147858
26. Hamrock, E., K. Paige, J. Parks, J. Scheulen, and S. Levin. "Discrete Event Simulation for Healthcare Organizations: A Tool for Decision Making." *Journal of Healthcare Management* 58, no. 2 (March-April 2013): 110–24, discussion: 124–5.
27. Sachidananda, M., J. Erkoyuncu, D. Steenstra, and S. Michalska. "Discrete Event Simulation Modelling for Dynamic Decision Making in Biopharmaceutical Manufacturing." *Procedia CIRP* 49 (2016): 39–44.
28. Troncoso-Palacio, A., D. Neira-Rodado, M. Ortíz-Barrios, G. Jiménez-Delgado, and H. Hernández-Palma. "Using Discrete-Event-Simulation for Improving Operational Efficiency in Laboratories: A Case Study in Pharmaceutical Industry. *Lecture Notes in Computer Science* 10942 (2018): 440–51. doi:10.1007/978-3-319-93818-9_42
29. Gunal, M. M. Simulation for Industry 4.0 [Internet]. 2019. http://link.springer.com/10.1007/978-3-030-04137-3, 1-16
30. Luscinski, S., and V. Ivanov. "A Simulation Study of Industry 4.0 Factories Based on the Ontology on Flexibility with Using Flexsim® Software." *Management and Production Engineering Review* 11, no. 3 (2020): 74–83.
31. Barlas, P., and C. Heavey. "Automation of Input Data to Discrete Event Simulation for Manufacturing: A Review." *International Journal of Modeling, Simulation, and Scientific Computing* 7, no. 1 (2016): 1630001. doi:10.1142/S1793962316300016
32. Rodič, B. "Industry 4.0 and the New Simulation Modelling Paradigm." *Organizacija* 50, no. 3 (2017): 193–207.
33. Rodríguez-Molano, J. I., J. A. Triana-Casallas, and L. E. Contreras-Bravo. "Modeling and Simulation of Integration of Internet of Things and Manufacturing Industry 4.0." *Communications in Computer and Information Science* 916 (2018): 231–41.
34. de Paula Ferreira, W., F. Armellini, and L. A. De Santa-Eulalia. "Simulation in Industry 4.0: A State-of-the-Art Review." *Computers & Industrial Engineering* 149 (2020): 149.
35. Sujova, E., H. Cierna, and R. Bambura. "Simulation Model of Production as Tool for Industry 4.0 Implementation into Practice." *Engineering For Rural Development* 18 (2019): 1192–7.
36. Lopes, M. R., A. Costigliola, R. Pinto, S. Vieira, and J. M. C. Sousa. "Pharmaceutical Quality Control Laboratory Digital Twin–A Novel Governance Model for Resource Planning and Scheduling." *International Journal of Production Research* 58, no. 21 (2020): 6553–67.
37. Morabito, L., M. Ippolito, E. Pastore, A. Alfieri, and F. Montagna. "A Discrete Event Simulation Based Approach for Digital Twin Implementation." *IFAC–PapersOnLine* 54, no. 1 (2021): 414–9.
38. Wikipedia. List of discrete event simulation software [Internet]. Wikipedia - The free encyclopedia. 2011. https://en.wikipedia.org/wiki/List_of_discrete_event_simulation_software
39. Dagkakis, G., and C. Heavey. "A Review of Open Source Discrete Event Simulation Software for Operations Research." *Journal of Simulation* 10, no. 3 (2016): 193–206.
40. Byrne, J., C. Heavey, and P. J. Byrne. "A Review of Web-Based Simulation and Supporting Tools." *Simulation Modelling Practice and Theory* 18, no. 3 (2010): 253–76.

About the authors

Pitoyo Amrih has more than 25 years of experience in the pharmaceutical industry with different roles in engineering and quality systems. For the past 12 years he has been a calibration, qualification, and validation projects leader at PT Konimex in Indonesia. He has a master's degree in the Department of Industrial Engineering at Sebelas Maret University, Surakarta, Indonesia. He holds a bachelor's degree in mechanical engineering from Bandung Institute of Technology. He served as an advisory board member in the Mechanical Engineering Department at Sebelas Maret University. Pitoyo has been an ISPE member since 2017.

Pringgo Widyo Laksono, DrEng, ST, MEng, is an associate professor in industrial engineering. In 2005, he joined as a researcher at the Production System Laboratory, Faculty of Engineering, Universitas Sebelas Maret, Indonesia. He received his Doctor of Engineering from Gifu University, Japan, in 2021. His research interests are automation and production development systems engineering, human–machine interaction, intelligent machine, human factors engineering, robotics, and control system engineering.

Investing in **People.** Building the **Future.**

Please consider making a charitable donation to the ISPE Foundation.

Your donation is needed to help fund key Foundation programs that positively impact patient populations across the globe both now and in the future.

WAYS TO DONATE

- Online at ISPEFoundation.org/donate
- Scan the QR code

ISPE® FOUNDATION

COLD SYSTEMS AS A SOLUTION to Decarbonize Water Purification

By Matias Navarro

The biotechnology and pharmaceutical sectors have pledged to reduce greenhouse gas (GHG) emissions as the climate concerns of consumers, investors, and regulators continue to grow. In seeking to benefit from this demand for sustainability and the potential for cost-saving opportunities, life science product manufacturers have started to evaluate the climate impact of their own labs and production facilities. This in-depth examination of the sectors' direct manufacturing processes uncovered one of the largest carbon emitters: water for injection (WFI).

DECARBONIZING WFI

A growing number of manufacturers have pledged to reduce these emissions through a commitment to achieving "net-zero," a state in which the GHGs entering the atmosphere is balanced by their removal from the atmosphere. Others are pioneering corporate initiatives to advance carbon neutrality ambitions well beyond emission sequestration and neutralization to eventually become fossil-fuel free. In either case, the achievement of these targets on time and on budget is based on the timely deployment of cost-effective energy efficiency and renewable energy projects. Crucially, WFI decarbonization is one of such interventions. Switching from hot to cold WFI systems converts the associated energy consumption from fossil-fired heat to electricity potentially powered by renewable sources, eliminating onsite combustion emissions and keeping the industry compliant with regulations and its own commitments to a net-zero future.

BACKGROUND ON CARBON EMISSIONS

The biotechnology and pharmaceutical industry, which is ranked high among the world's largest carbon emitters and is responsible for 197 tonnes of carbon dioxide equivalent (tCO_2e), presently ranks 15th on the list of highest emitters, outpacing the emissions of other carbon-intensive industries like semiconductor manufacturing and forestry and paper products [1]. The calculation of emissions from Scope 1 and 2 (i.e., emissions from direct on-site and indirect purchased energy) shows that the global pharmaceutical sector is 55% more greenhouse gas intensive than the automotive sector [2]. This means that cars, vilified for their global warming potential, are greener than medicines when it comes to manufacturing.

The pharmaceutical industry will need more life science professionals—from facility designers to pharmaceutical engineers—to address the impact of the industry's internal manufacturing operations. These operations will be a crucial lever for contributing to the carbon savings that most pharmaceutical and biotechnology companies have committed to deliver (see Figure 1).

The industry has a unique opportunity to examine its own direct manufacturing impact. In doing so, it may uncover legacy, carbon-intensive operations that can be replaced with technologies that deliver the same consistent regulatory compliance and microbiological safety assurances with higher energy efficiency and using more clean energy sources for improved environmental performance.

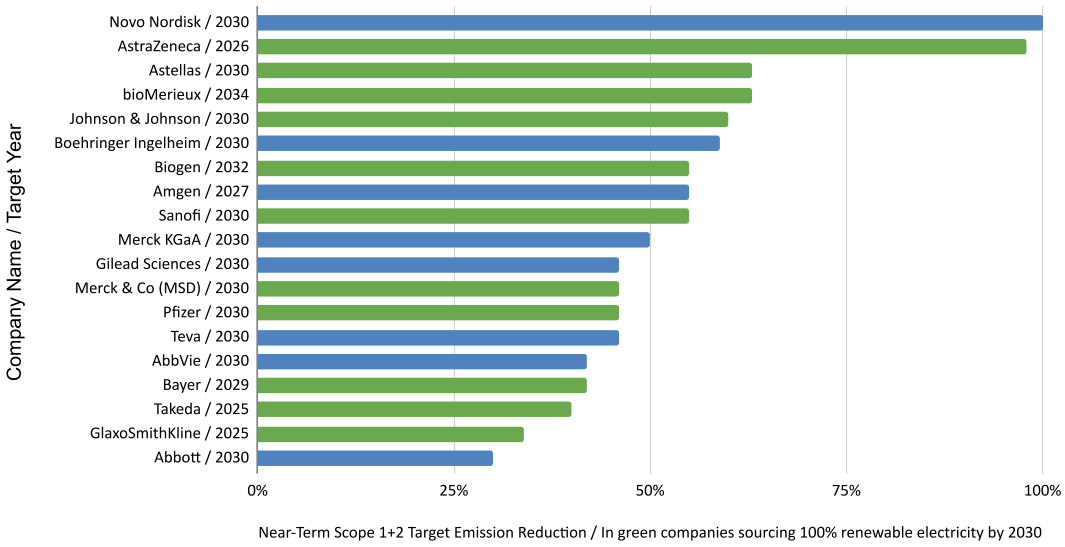
WHAT IS THE PURPOSE OF WFI?

WFI, obtained through a further purification of pharmaceutical purified water, has the highest purity and sterility. It also has one of the largest carbon footprints associated with drug manufacturing and bioprocessing. WFI has played a critical role over time in enabling a multitude of core pharmaceutical processes—from the preparation of irrigation solutions to the production of small-molecule active pharmaceutical ingredients (APIs) used in parenteral medicines.

Beyond these traditional uses, WFI has also become an essential commodity in the making of biological drugs derived from cells cultured in bioreactors, biotechnology research, and biomanufacturing. It can also be used for contaminant-sensitive biological needs, such as rinsing for cleaning production vessels and equipment, diluting buffers for chromatographic purification, hydrating dry powder media for growing microorganisms, and preparing solutions for actual products for injection, such as vaccines and advanced therapy medicinal products.

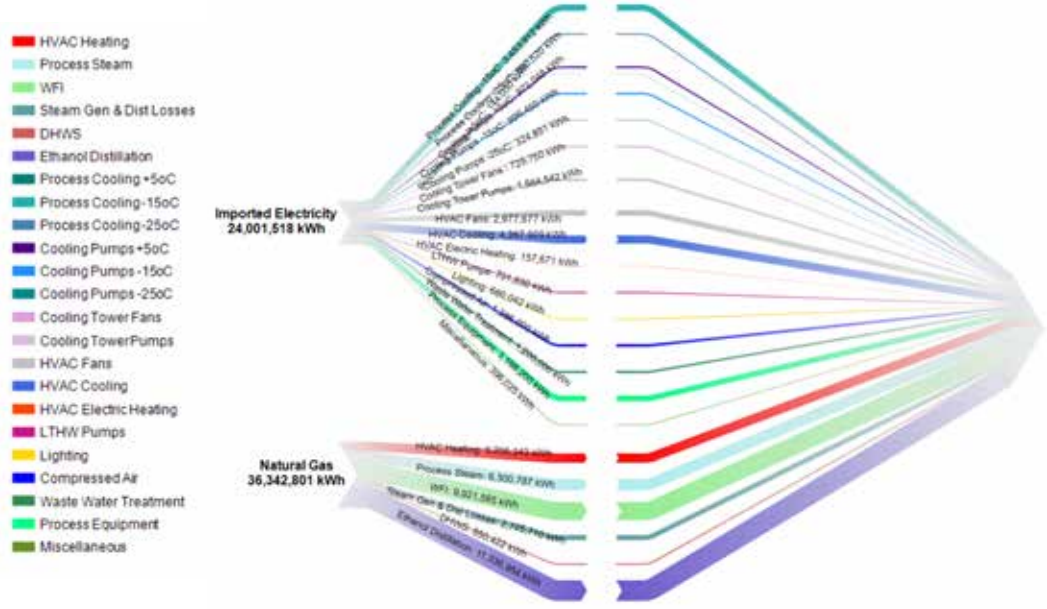
Rapid advances in biomanufacturing with tight specifications for microbiological purity and the absence of endotoxins have exposed the need to provide greater volumes of WFI, an essential commodity that is as critical to biomanufacturing as it is to its

Figure 1: Climate targets of global pharmaceutical, biotech, and life-sciences companies.



Source: Veolia research based on validated targets by science-based targets initiative (SBTi).

Figure 2: Sankey energy flow diagram showing a case of WFI as one of the largest users of high-temperature steam.



Reproduced with permission of EECO2.

decarbonization plans. The need for generating larger volumes of WFI, boosted by the pandemic-driven race to produce COVID-19 vaccines, has made it the biggest driver of critical utility usage—and therefore energy input, spending, and emissions.

WFI CARBON EMISSIONS

Energy mapping, the visual representation of energy demands within a facility, shows that it would be most advantageous to curb the largest energy loads. For critical utilities, it means first reducing WFI demands. After all, WFI should only be used in those applications for which it cannot be replaced with a lower-emission substitute, such as purified water. But this step alone is not enough.

For the longest time, WFI generation has been dominated by long-lived, capital-intensive distillation equipment that uses a lot of energy in the form of thermal heat produced by fuel-fired, combustion-based systems, called stills (see Figure 2). Stills, which produce large amounts of emissions, cannot be easily decarbonized. Since their introduction in the 1970s, stills have

Solutions that include cold and ambient temperature could easily supply the majority of global WFI needs once regulators and industry embrace greener technology that aligns with carbon emission reduction goals and cost savings.

become so pervasive and energy intensive that they are now the top contributor to clean utility emissions and, thus, a key obstacle to achieving substantial carbon savings.

The high-energy intensity of "steam machines" [3] is, unfortunately, hardly surprising. By essentially boiling large amounts of water, distillation relies on the transfer of massive amounts of thermal energy input (i.e., process steam) to vaporize the feed water and achieve the phase transition from water to steam. Thus, the key to the purity of WFI is in this phase change that ensures that particles, endotoxins, pyrogens, and other contaminants are not carried along during the subsequent condensation and cooling steps.

Multiple-effect (ME) distillation, the most expensive and carbon-intensive WFI production technique despite all its advances in heat recovery, surprisingly remains the most dominant WFI purification method globally. Vapor compression (VC), an electrically assisted distillation technology with much lower steam demands, is less carbon intensive. VC and ME distillation account for at least one-fifth of on-site combustion-related emissions and at least one-tenth of average total energy demand [4].

WHY IS REFORM NOW POSSIBLE?

Distillation did not become the exclusive form of WFI purification by accident. Following decades-old requirements, regulators in charge of safeguarding the sterility in diagnostic, therapeutic, and parenteral drug products had restricted WFI production to heat-based distillation. Regulators still believed that only heat-based distillation with a phase change could guarantee absolute chemical and biological quality. For pharmaceutical products to be traded internationally, they had to be produced in facilities generating hot WFI, the method in accordance with most international pharmacopeias. This made alternative means of WFI production difficult and fraught with risks.

The development of current distillation methodology reveals why the shift from hot to cold WFI production is inevitable. First, regulators are not running behind anymore. They have caught up with technology, energy conservation, and decarbonization needs. Since 2017, all national pharmacopeias except for Chinese pharmacopeias have allowed global drug and therapy makers to produce WFI using purification methods other than distillation [5].

Second, technology providers have the energy-efficient solutions needed to address the challenges of water purification without high-temperature heat and the emissions derived from fossil fuel combustion. Third, regulation is aligning with the need for renewable energy deployment, and market economics also point toward a carbon-constrained future with higher carbon taxation and lower electricity costs due to the rapid decarbonization of on-site energy sources [6] and national electricity grids. This has contributed to a shift in WFI production from natural gas–fired steam boilers to greener all-electric WFI systems at ambient temperature.

Cold WFI membrane systems, a greener technology that has yet to be fully adopted, are estimated to meet no more than one-fifth of the new WFI needs [7]. Solutions that include cold and ambient temperature could easily supply the majority of global WFI needs once regulators and industry embrace greener technology that aligns with carbon emission reduction goals and cost savings. Hot WFI could be phased out considering the following:

- The efficiency of stills is unlikely to significantly improve as the industry has pushed their operational limits for decades making them, more likely than not, as efficient as they can possibly be.
- Steam generation has gained productivity over time through waste heat recovery and condensate return. But soaring fossil fuel prices and the potential for carbon taxes also increase the costs of steam-heated distillation.
- The adoption of large electric boilers that could decarbonize steam generation is hindered by much higher operating costs compared to those of fossil fuel–fired boilers, as the weighted average electricity price is almost four times higher than the average price of natural gas for the same unit (joule or kilowatt equivalent) of energy.

These points, along with the pressures of the environmental, social, and governance (ESG) [8] movement driving net-zero strategies, are reinvigorating the way companies approach decision-making around the energy-related emissions of WFI generation assets—80% of which rely on steam produced by the combustion of fossil fuels, either natural gas or other hydrocarbons [7].

COLD WFI SYSTEMS: REVERSE OSMOSIS

Reverse osmosis (RO), a process that rejects ions using an applied pressure to force water through a semipermeable membrane, introduces reduced energy costs compared to thermal techniques. Unlike steam-heated distillation, RO is a physical process that involves neither high temperatures nor phase changes. Thus, it became known as cold, or ambient, WFI when followed by an additional downstream module and membrane barrier to produce pharmaceutical water of the highest purity and sterility.

Engineers and critical utility managers unfamiliar with cold WFI systems may ask whether membrane systems are new and, therefore, risky. They are neither. RO has long been the technology of choice for demanding applications such as ultrapure water production for semiconductor manufacturing. In the pharmaceutical industry, membranes have produced US Pharmacopoeia and European Pharmacopoeia Purified Water and the now-defunct European Pharmacopoeia Highly Purified Water grades since the mid-1980s and early 2000s, respectively.

Since then, RO cleaning operation procedures have been perfected with sanitary construction, advances in hygienic system design, and the emergence of temperature-resistant polyamide material. This has enabled the use of hot water sanitization to inactivate microbes and control fouling and biofilm formation without the addition of chemical agents.

Compared to hot systems, cold WFI consumes up to 50% less electricity than VC distillation and less than one-tenth of the overall energy use per produced volume than ME distillation [9]. The environmental advantages of cold WFI technology begin with the operation philosophy itself. For starters, this process converts any source of softened, dechlorinated drinking feed water into WFI through a sequential, continuous purification process. That process features electric-driven pumps and a membrane barrier integrating RO, chemical-free continuous electric deionization, and ultrafiltration.

Unlike thermal distillation, water filtration through membranes does not require generating steam or changing water phases, both very carbon-intensive processes. Instead, high-pressure pumps force the water through the membrane system, generating more modest CO_2 emissions. To further reduce them, pumps are equipped with variable frequency drives. These devices adjust the membrane feed pressure to fluctuating levels of demand in real time by automatically and instantaneously controlling frequency and voltage to the motors. This saves time and electricity demands by as much as 20% while extending the system's lifetime and avoiding costly breakdowns [10].

REDUCING RISKS AND COSTS

No WFI generation system, no matter how energy efficient, will succeed if it doesn't control microbiological risk and maximize water recovery while minimizing workforce interventions. Membrane-based generators address these challenges with new and enhanced features.

First, to meet the need for bioburden and endotoxin control derived from the higher microbial risk of operating at ambient temperatures, hot water sanitization is a safe and effective practice that also optimizes the flow through membranes by preventing scaling and fouling. The amount of energy for heating to 80°C is relatively low compared to the continuous steam demand for distillation or storage heating [11], and an electric heater or heat pump powered by renewable sources can sanitize the system with hot water and zero emissions.

Second, ultra-high volumetric recovery rates minimize the water footprint, particularly in areas with water stress or tight limits on wastewater discharge permits. This is done by recirculating the RO concentrate through another stage equipped with temperature and pH control devices to reduce the wastewater volume drained by up to 50%. Third, cold WFI production, membrane cleaning, and system maintenance operations are optimized with additional monitoring and sampling hardware to control risk and performance through real-time analytics and data-driven process automation to save energy and costs.

ADDITIONAL BENEFITS OF COLD WFI

Cold WFI energy savings extend beyond the generation step. Storage tanks, designed to compensate for the peak in WFI demands, and distribution pipelines, which circulate WFI from the storage tank to the consumption points, can also be designed to eliminate the heating and cooling steps typically required for hot WFI before utilization.

The easiest way to upset the quality of WFI systems is microbial activity getting out of control, particularly bacterial growth in storage tanks and distribution loops. Operating them under hot temperatures has been a popular antidote to keep bioburden at bay. But continuous recirculating, self-sanitizing hot water

systems, which today represent more than 70% of the total WFI installed capacity [12], come at the cost of increasing already bloated steam-related costs and emissions.

But the problem goes beyond energy consumption. In GMP environments, most WFI applications other than cleaning—which have been all but eliminated in facilities with single-use systems—require ambient WFI, particularly when biological products suffer thermal degradation above 25–30°C [13]. In addition, the required cooling mechanism necessary to protect the integrity of biological processes and the safety of users is an energy guzzler and a source of endotoxin and bacterial contamination [14]. An additional operational efficiency of cold WFI systems is that hotter systems are associated with greater rouging and shorter longevity due to faster wear of some mechanical components.

In short, suppressing microbial proliferation through high-temperature circulation may be operationally questionable and financially and environmentally irresponsible in the face of the industry's commitment to achieving cost-efficiencies and net-zero targets.

To eliminate thermal energy consumption while controlling bacterial potential, forward-looking utility designers also favor ambient temperature storage tanks and loops sanitized through continuous injection of ozone, which is designed to be depleted via radiation before distribution. With appropriate contact time, ozone produced either by electric discharge or electrolytically, for example, ensures WFI delivery at the temperature required for most biopharmaceutical uses. At the same time, it delivers substantial savings in capital investment as it avoids the complexity of the heating and cooling loops and the installation of multiple coolers at each point of use [15]. For those limited uses in which hot water is preferable, a reduced hot sub-loop operating above 65°C ensures microbial destruction while requiring smaller heat exchanging capacity.

According to the Parental Drug Association (PDA) [12], only about 10% of installed systems in operation feature a low-temperature approach to WFI storage and distribution. Energy and carbon constraints, as well as cost efficiencies, may be changing that. Not surprisingly, ambient designs are growing fast. They are five to seven times less expensive and up to 80% less polluting than maintaining hot storage and distribution loops. These benefits reinforce membrane-based WFI's long-standing price edge over distillation-based generation, an advantage that is even greater with an end-to-end cold WFI solution in which the making, storage, circulation, and usage are all at the same ambient temperature.

ENERGY TRANSITION TO WFI TRANSITION

Aside from regulatory drivers, the emergence of membranes for WFI is an unintended consequence of the convergence of two forces: the ambition to reach net-zero emissions and economic factors. As the industry pushes toward a decarbonization of distributed technologies, such as energy storage and microgrids, the need for all-electric cold WFI generation makes membrane technology a plausible solution to meet zero-emission targets.

However, economic pressure is equally effective at driving the transition to cold WFI. For engineers and managers of clean utilities, switching to cold WFI helps them do more with less: delivering the same consistent WFI quality inside the loop and at the point of use with higher energy savings and lower utility costs. At the same time, they take on a modestly higher level of microbiological risk. These risks, which can be efficiently managed through a holistic process and quality control strategy, are handsomely rewarded. The trade-off allows facilities to move closer to net-zero targets, reduce grid reliance, eliminate exposure to fuel price volatility, stabilize energy costs, and boost resiliency and energy security.

ELECTRIFIED WFI IMPROVES CLEAN POWER GENERATION

When paired with expanding renewable energy sources, electrified cold WFI systems allow facilities to become closer to eliminating carbon emissions altogether. This unique proposition leverages the pledges of many global pharmaceutical and biotechnology companies to run 100% of their plants on a fully decarbonized electricity supply. Their investments—either through purchasing from adjacent off-site renewable sources or by integrating on-site demand management, storage, microgrid, and distributed solar generation [6]—are important in significantly lowering electricity costs. This is a key to the competitiveness of electrified solutions along with the implementation of carbon pricing, a practice already adopted by many pharmaceutical giants to shape their future investment decisions [16].

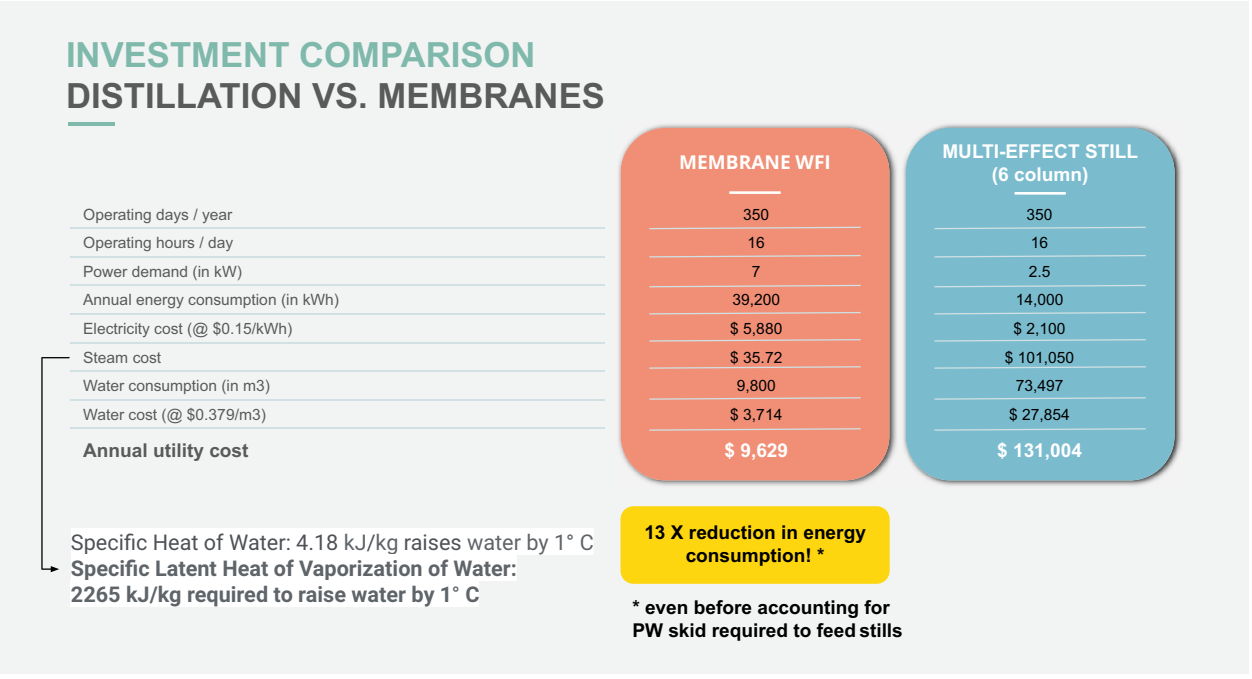
Just as pure water decarbonization impacts clean energy production, membrane-based technologies will also be impacted by future carbon-neutral building codes for industrial plants in the US and Europe [17, 18]. These codes will help ensure a very high-energy performance and zero on-site combustion emissions. This union of net-zero building standards, ultra-efficient pure water systems, and clean electricity solutions will be at the core of corporate climate strategies.

GETTING STARTED WITH LOW-CARBON WFI

As demonstrated by the differences between hot and cold WFI, it is unequivocal that membrane systems are a clear short-term answer to the current energy crisis. They are natural candidates for installation during capacity expansions and newly constructed energy-efficient facilities. However, this alone will not be enough. As we look to a net-zero future in which all facilities are part of this effort to transition to clean-powered cold WFI technology, the top-of-mind question is "where to start and how can we pay for it?" After all, unless modern, electrified replacements for hot WFI are chosen, we will continue to need difficult-to-decarbonize steam heating, making net-zero goals more difficult to reach.

The first step is to focus on the retrofit of WFI systems that are outdated but not old enough for replacement. It's unlikely that manufacturers will replace high-cost purification equipment unless it's nearing the end of its lifespan, which for distillation units can be up to 20 years [17]. For plants that can afford the capital

Figure 3: Annual utility costs of membrane filtration vs. ME distillation for WFI production [19].



expense, the installed costs for cold WFI relative to potential savings on energy spending (e.g., when switching from hot to cold WFI) often mean that membrane systems are less expensive within periods as short as four years, thanks to their much higher energy performance, which offsets the upfront cost over time. The payback period shortens considerably if integrating lower clean energy costs and higher carbon taxes.

Short of making the outright investment in cold WFI equipment, one way for facilities to make WFI retrofits financially attractive to the balance sheet is by leveraging budget-neutral strategies. With this type of strategy, a portion of the savings of eliminating steam demand are diverted from the existing utility budget to finance a loan that pays for the WFI system upgrade. Under this plan, facilities take advantage of reduced operational spending, no upfront capital outlays, and full ownership of the equipment, which continues to accumulate energy savings that compensate for the cost of the retrofit after the loan repayment.

Another alternative is a model known as Water-as-a-Service. This is as a pay-per-use program that allows facilities to benefit from on-site cold WFI production with uptime guarantees and without upfront investments while offloading responsibility for maintenance schedules, operational risks, and regulatory compliance onto the equipment supplier and service provider.

COLD WFI MAKES GOOD BUSINESS SENSE

Because of tighter margins and growing competitive pressures, the industry has been driving manufacturing cost-efficiency for years. With surging energy costs, modernizing WFI production is far from the only initiative to rein in spending and emissions, but it is a quick win that can deliver significant reductions in critical utility emissions.

The recent rise in energy costs may have been a blow for pharmaceutical engineers mulling over ways to limit utility expenses. Instead, it should be a wake-up call to provide equipment vendors with clear energy use guidance through user requirement specifications that help them achieve optimized equipment designs. As long-lived, energy-intensive assets are locking future costs and emissions for 20–30 years, we should all think long and hard about how the impact of our decisions may contribute to higher, not lower, emissions in the future. To be sure, net-zero targets can't afford the installation of new stills that rely on boilers burning fossil fuels until mid-century.

The efficient, electric solutions to break free from legacy WFI technology are affordable. And their economic benefits are also inarguable. From a capital expense perspective, they are up to 43% cheaper than equivalent stills, which take a higher level of pretreatment and thus, have a larger carbon and physical footprint. From an operational point of view, the savings can be even larger depending on system capacity, utility costs, etc.

Optimizing for the smallest energy, carbon, and physical footprint isn't just a win for the environment. It is good for business too, with clear operational and financial benefits. Other valued business benefits—such as enhanced reputation, goodwill, and trusted relationships with employees, consumers, and investors

who track the progress of companies through rating systems such as Carbon Disclosure Project and Global Real Estate Sustainability Benchmark—may be more intangible but are just as critical.

WHAT WILL A TRANSITION ACCOMPLISH?

Ultimately, the choice between cold and hot WFI systems for drug makers becomes a decision about costs. The difference lies in when, how much, and how often they will pay. Although the annual costs of inaction are not visible, they do accumulate for the planet and the bottom line. The longer pharmaceutical and biotechnology companies wait to mitigate energy price volatility, the greater their climate, insurance, market, credit, and, above all, reputational risk become. Planning and managing a climate-resilient future has become essential. Companies either act on the transformations they committed to or risk stakeholders forcing those transformations upon them. Consumers, investors, regulators, and employees are all calling for more accountability from companies when it comes to adopting sustainable manufacturing practices.

CONCLUSION

From the industry's earliest days, and especially throughout the pandemic, pharma professionals have been at the forefront of science, advancing our understanding of disease, developing new and innovative treatments, and moving those treatments into production at warp speed.

Our best shot for delivering on the pledge to reach net-zero emissions is to use the same exceptional strengths that brought the scientific, industrial, and logistical achievements that culminated with the swift deployment of multiple effective COVID-19 vaccines and therapies—catalyzing the hope of billions of people around the world. Membrane-based systems offer a ready starting point for safer, cleaner, leaner WFI generation. It's time to turn the tide and muster the same passion, purpose, and urgency to propel the decarbonization journey ahead of us.

United again around the net-zero goal, pharmaceutical engineers should build on the same resolve and immediate response that helped the world through the pandemic. To be sure, it will not be easy. The size, speed, and scope of the change can be daunting as processes and technology aren't typically replaced on a dime. But we need not wait three decades to start. The sooner a proactive transformation of critical utilities starts, the better the chances of succeeding before 2050 and avoiding a more reactive, more expensive energy transition.

References

1. My Green Lab and Urgentem. "The Carbon Impact of Biotech and Pharma." October 2021. www.mygreenlab.org/blog-beaker/my-green-lab-measures-carbon-impact-of-biotech-and-pharma
2. Belkhir, L., and A. Elmeligi. "Carbon Footprint of the Global Pharmaceutical Industry and Relative Impact of Its Major Players," *Journal of Cleaner Production* 214 (20 March 2019): 185–194. doi.org/10.1016/j.jclepro.2018.11.204.
3. Multhauf, M., "Cold WFI Manufacture - Two Years after the Change in the Pharmacopeia." *GMP Journal*. 15 January 2020. www.gmp-journal.com/current-articles/details/cold-wfi-manufacture-two-years-after-the-change-in-the-pharmacopoeia.html.
4. Gibson, A. B., "Sustainability: Toward Zero Carbon in the Pharmaceutical Industry." *Pharmaceutical Engineering*. March/April 2020. https://ispe.org/pharmaceutical-engineering/march-april-2020/sustainability-toward-zero-carbon-pharmaceutical
5. International Society for Pharmaceutical Engineering. *ISPE Good Practice Guide: Membrane-Based WFI Systems.* Table 2.1. North Bethesda, MD: International Society for Pharmaceutical Engineering. 2022.
6. Kansteiner, F. "The Energy Switch: Big Pharma Harnesses Sun, Wind and Water in Quest for a Low-Carbon Future." *Fierce Pharma.* 15 October 2021. www.fiercepharma.com/pharma/solar-wind-water-pharma-go-planet-astrazeneca-novo-nordisk-novartis-and-amgen-talk-renewable
7. Global Water Intelligence. "Resilient Pharmaceuticals Industry Presents Robust Water Opportunities." *Global Water Intelligence Magazine* 22, no. 3 (25 March 2021). www.globalwaterintel.com/global-water-intelligence-magazine/22/3/general/resilient-pharmaceuticals-industry-presents-robust-water-opportunities
8. Gsell G., C. Nunez, K. Klein, and B. Essary. *WFI: A Cost Review, A Cost Evaluation of Alternative Systems for Producing Water for Injection (WFI), Including Membrane-Based WFI Production Absent Distillation.* MECO, 7 June 2019. https://s20791.pcdn.co/wp-content/uploads/2018/09/MECO-Water-for-Injection-A-Cost-Review-002-1.pdf
9. Gyllensten, F., and A. Castagnini. "Saving Energy with VSD Systems." *Hydrocarbon Engineering* (February 2019).
10. CFA Institute. "ESG Investing and Analysis." CFA Institute. Accessed 27 June 2022. www.cfainstitute.org/en/research/esg-investing
11. Cataldo A. L., B. Sissolak, K. Metzger, K. Budzinski, O. Shirokizawa, M. Luchner, A. Jungbauer, and P. Satzer. "Water Related Impact of Energy: Cost and Carbon Footprint Analysis of Water for Biopharmaceuticals from Tap to Waste." *Chemical Engineering Science: X* 8 (November 2020). doi.org/10.1016/j.cesx.2020.100083
12. Landsberg, M., "Ozone in PW and WFI Storage Systems," PDA Israel. May 2019. http://pdaisrael.co.il/050519/Ozone%20in%20PW%20&%20WFI%20Storage%20Systems.pdf
13. Odum, J., and M. C. Flickinger. *Process Architecture in Biomanufacturing Facility Design.* Hoboken, NJ: John Wiley & Sons Inc., 2018. 276–279.
14. Sandle, T. "Design and Control of Pharma Water System to Minimize Microbiological Contamination." *Pharmaceutical Engineering* July/August 2017. https://ispe.org/pharmaceutical-engineering/july-august-2017/design-control-pharma-water-system-minimize
15. Cohen, N., and B. L. Johnson, "Performance and Validation of Ozone Generation for Pharma Water Systems." *Pharmaceutical Engineering* July/August 2017. https://ispe.org/pharmaceutical-engineering/july-august-2017/performance-validation-ozone-generation-pharma-water
16. Clark, P. "More Companies Put Price on Their Carbon Emissions." Financial Times. 19 September 2016. www.ft.com/content/722f5df2-7e7f-11e6-8e50-8ec15fb462f4
17. US Department of Energy. "Low Carbon Pilot Toolkit." Better Buildings. Accessed 27 June 2022. https://betterbuildingssolutioncenter.energy.gov/challenge/special-initiatives/low-carbon-pilot
18. European Commission. "Nearly Zero-Energy Buildings." Accessed 17 Jun 2022. https://energy.ec.europa.eu/topics/energy-efficiency/energy-efficient-buildings/nearly-zero-energy-buildings_en
19. Monnier, F. "EPPI Membranaire: Une Solution Ècologique et Èconomique?" Pharmacos Media, 6 October 2022. www.pharmacos-media.fr/actualite/produisez-votre-eppi-tout-en-reduisant-votre-empreinte-environnementale-52462.html

About the author

Matias Navarro is Business Development Director with Veolia Water Technologies where he designs sales and marketing strategies that identify target markets, achieve product fit, and establish the business model to drive customer acquisition. He leverages a unique combination of in-depth strategic analysis and market research to grow a portfolio of mission-critical water processing systems with a particular focus on energy efficiency and reduced life cycle costs. With his broad knowledge of the industry value chain and deep domain expertise in treatment processes, he executed strategic partnerships and implemented channel management tools to improve competitive positioning and optimize growth opportunities. Matias holds a Bachelor of Science in civil engineering and a master's degree in business administration. He joined ISPE in 2021.

USING INDUSTRY SURVEY DATA to Shape Cell Therapy Facility Design

By Allan Bream and Jan Bondoc

Cell therapies have been used to treat thousands of patients worldwide ever since the CAR T cell medication Kymriah was the first cell therapy approved by the FDA in 2017 [1]. Yet significant manufacturing challenges continue to hamper patient access to life-saving cell therapies, particularly the high cost of these treatments. Kymriah can cost as much as $475,000 per dose [2] and an allogeneic cell therapy for metachromatic leukodystrophy (MLD)—which was approved by the UK's National Health Service—comes with a $3.9 million price tag [3]. Other cell therapies have been removed from the European market because of similarly high prices.

We gathered insight from more than 300 industry experts through our CRB Horizons: 2022 Life Sciences report [4] to inform a vision for cell therapy facility design that can help address this and other challenges. Cell therapies hold incredible promise to treat previously incurable conditions such as cancers and autoimmune disorders. But they come with unique challenges, owing to the personalized nature of the treatments—one patient per treatment for autologous cell therapy. Manufacturing such small batches requires specialized equipment and skilled operators.

These were among the weak points that industry experts identified when we asked them about successful cell therapy manufacturing for *CRB's Horizons: 2022 Life Sciences report* (see Figure 1) [4]. To broaden patient access to these curative therapies, any solution to the challenges of cell therapy manufacturing must reduce costs.

In this article, we will discuss how designing flexible, commercial-ready facilities is important to address three of the many challenges:

- Attracting and retaining talent
- Lowering overall cost of goods
- Preparing for a smooth technology transfer

Specifically, the solutions include:

- Adopting a platform-based approach to improve scalability
- Improving readiness for a point-of-care model

Together, these will go a long way to alleviating the significant roadblocks to patient access.

ATTRACTING SKILLED STAFF IN A COMPETITIVE ENVIRONMENT

The scientists and technicians who work to provide curative cell therapies continue to be among the most important resources in all pharmaceutical manufacturing. Yet when industry experts were asked to list weak points in successful cell therapy manufacturing, 55% chose lack of trained staff (see Figure 1).

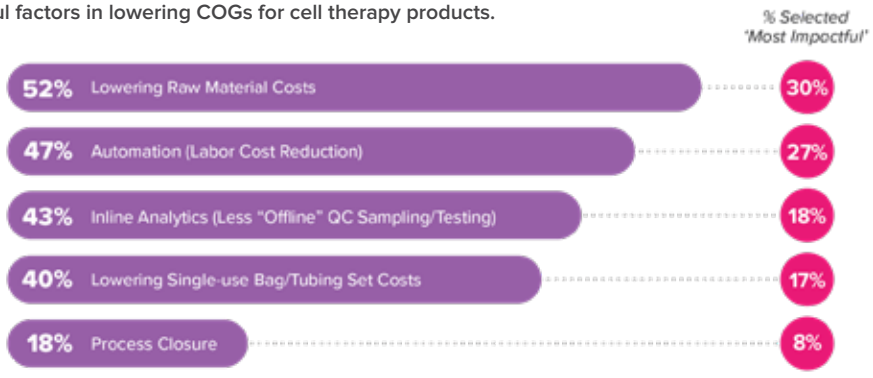
This is largely because of the unique technologies and processes used in cell therapy manufacturing. Even for manufacturing operators with experience making traditional biologics, the different skills require significant retraining. The tremendous competition to attract and retain good operators means successful companies will need to differentiate beyond the standard offerings of competitive salary and benefits.

Designing facilities that are vibrant and pleasant and that promote the positive aspects of the science and culture of producing curative therapies can create an environment that skilled operators will want to work in. This is a conservative industry, where tradition and perception have been set, and costs usually eclipse other factors. But when companies pay attention to the aspects of design that affect staff, they can improve facility functionality, increase productivity, and reduce human error. Here we outline some ways to use design to improve worker experience and a facility's function.

Figure 1: Experts were asked "Do you see any of the following as a weak point in successful cell therapy manufacturing [yes/no]."

Figure 2: Examples of cleanrooms that incorporate windows and colored walls.

Figure 3: Most impactful factors in lowering COGs for cell therapy products.



Provide a Vibrant Workplace

Years ago, it was not uncommon to construct a cell culture process facility with prefabricated concrete panels and no windows, which led to a degree of frustration and burnout for employees. Designing a facility in which people are happy to work might mean, instead, ensuring visual connections between rooms and the outside, as well as expanding the traditional color palette.

These are easy ways to improve the way spaces function and the overall working environment (see Figure 2). For example, although white connotes sterility and cleanliness, there are no regulations stating that cleanrooms must be white. Designing an attractive facility could also require investing in a region where real estate and construction costs are higher per square foot—if that location fosters creativity.

Staff will be more productive when they have access to decent amenities, such as a library, an attractive cafeteria/break area, and a natural setting to meet outside. Given the collaborative nature of science, it makes sense to have a pleasant space for people to get together and share their challenges and ideas.

Design for Wellness and Productivity

Cell therapy facilities continue to rely on manual operations, performed by numerous staff who must spend large parts of their workday in gowns, gloves, masks, and safety glasses, often in rooms with little daylight and no exterior views. This can be disorienting and adversely affect physical and mental health. Providing windows to bring in light and sightlines to the outside improves a workspace.

Celebrate the Science and Culture

Creating visual connections between corridors or other spaces and the manufacturing suites can spark excitement about the science. Adding windows to walls within the facility can provide views into the inner workings of the facility for visitors and employees.

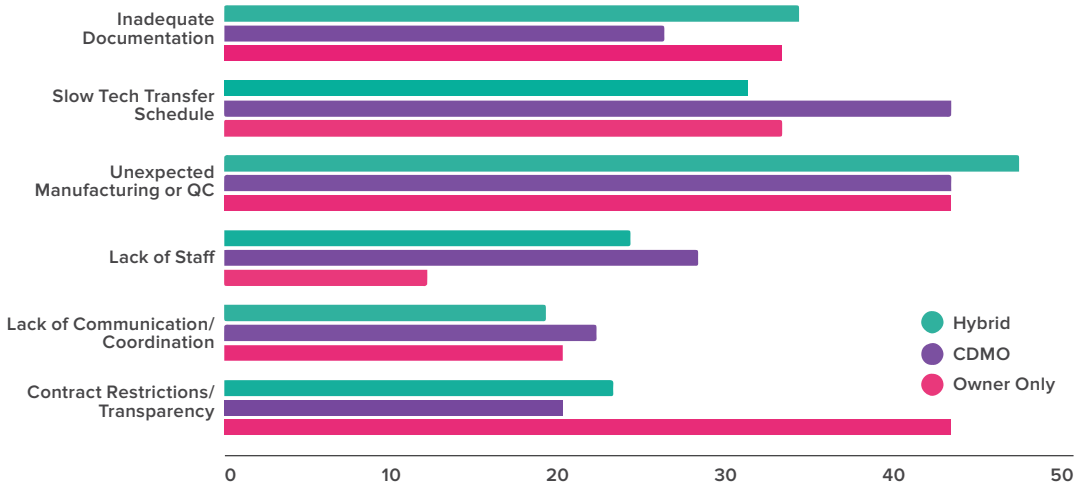
Good design blurs the lines between functional spaces to promote collaboration and visual communication. Inclusivity between functional work teams can bring together the PhD scientists and operators with non-manufacturing staff to allow people to learn about the science happening in their facility.

LOWERING THE COST OF GOODS

What can life-changing therapies do if we cannot get them to the patients in need? Reining in costs at every opportunity can go a long way to making effective cell therapies more accessible. Among the most impactful factors to lower cost of goods (COGs) that we, as designers, can support are process closure costs and automation (see Figure 3).

The equipment used in research and development labs and for clinical trial production involve manual processes with open

Figure 4: The most impactful issues for cell therapy technology transfer.



connections performed in a Grade A biosafety cabinet with Grade B room background classification. Manual, open manipulations have a greater risk of failure, and high failure rates increase costs. Scaling this approach to meet commercial capacity can have inherent risks that increase with scale.

Design can help COGs through automation and process closure. A thorough analysis of the process will allow a determination of how to reduce risk while procuring, or designing, the appropriate equipment.

The Advantages of Process Automation and Process Closure

We found it surprising that only 18% of survey respondents identified process closure as an impactful strategy to decrease COGs. Cell therapies cannot be sterilized, meaning cell therapy manufacturers use aseptic processing to protect the quality and safety of their products and comply with applicable regulatory requirements. Because there are synergies between automation and process closure, our experience shows that both must be explored to find their full potential.

Process closure is key to scaling cell therapy manufacturing and can result in significant cost savings. The move away from open, manual processing reduces cleanroom classification, minimizes staffing requirements, and lowers the risk of cross-contamination. In addition to the advantages for manufacturing, process closure helps reduce the footprint needed for supporting functions, such as gowning and environmental monitoring. It is best to consider these process and equipment needs early so they align with the company's manufacturing objectives.

Likewise, system automation is becoming essential for commercial success. Pharma 4.0™ has encouraged the industry to swap manual operations for automated manufacturing technologies. Regulatory agencies want companies to apply the best available technologies and anticipate future developments. Pharma 4.0™ addresses data capture and analysis, as well as inline analytics, aspects that can instill confidence in regulatory agencies regarding the commercialization of these therapies. Data can be collected, analyzed, and applied to adapt and improve processes without extensive disruptions. When the closed processing equipment leads to a lower room classification, and this is combined with the reduction in labor needs through automation, these two factors have the synergistic effect of driving down operating expenses.

PREPARING FOR SMOOTH TECHNOLOGY TRANSFERS

GMP manufacturing requires the necessary capital, facilities, and trained staff, which may be unavailable to a company with a promising drug candidate. For these reasons, a company is likely to turn to a contract development and manufacturing organization (CDMO) for process development and early-stage manufacturing. Fortunately, half of survey respondents noted that transferring the technology from an innovator's research and development facility to commercial manufacturing at a CDMO was a smooth process. This reflects the trend toward a more collaborative approach between partners that co-develop processes.

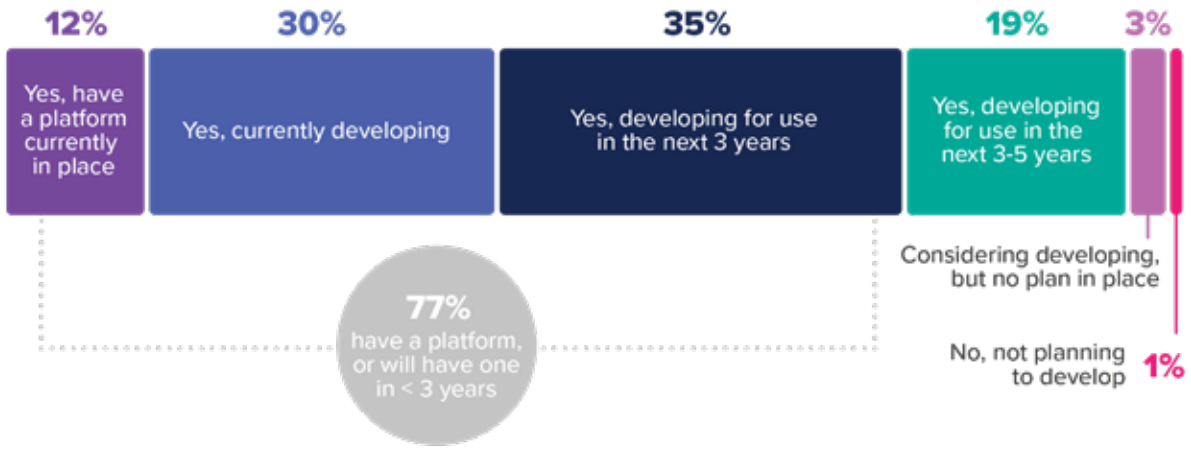
However, although only 12% of overall respondents disagreed that technology transfers were smooth; that percentage was higher among sponsor companies. They noted unexpected manufacturing changes and a lack of transparency as the most impactful issues (see Figure 4).

Unexpected manufacturing changes can occur when a CDMO continues to improve a process during development and these improvements are either not communicated to or cannot be accommodated by the client company. Problems like this can be reduced with transparency and good communication. A good example would be a sponsor company lacking the necessary technology and methodologies that a CDMO can provide.

Design in Flexibility

Designing for flexibility in the manufacturing layout can help accommodate unexpected changes and anticipate technological

Figure 5: Development of a cell therapy platform process.



innovations that may evolve. Ideally, the company can rely on this roadmap to design the current process, then make future changes without investing in a complete redesign or renovations. In addition to automation and process closure, flexible design considers what equipment would need to be switched out by anticipating move-in and move-out paths, allowing changeover without having to alter the facility's core structure.

Flexible design could include a Grade B cleanroom to accommodate an open process. Companies progressing toward a closed process may find themselves in transition and still needing aseptic processing suites for certain manufacturing steps that remain open, such as the preparation of custom tubing assemblies or small-volume sterile solutions.

Given the time-sensitive nature of cell therapy manufacturing, one way to reduce risk and increase flexibility is to bring the quality control test lab closer to manufacturing. When determining which assays will be accommodated in house vs. outsourced, companies should consider the sample handling and logistics involved, as well as the increased risks and duration of product release.

When sponsor companies and CDMOs work together, they can develop scalable, patient-focused manufacturing strategies that alleviate many technology transfer woes. Two notable trends that forward-thinking partners are embracing are developing a platform process and point-of-care manufacturing.

ADOPTING PLATFORM PROCESSING TO SCALE OUT

Although the steps for each cell therapy process are often similar—for example, genetic material in a virus is transduced into a patient's cells—the process, equipment, and vectors used for each treatment can be unique. The choice of vectors is diverse and includes viruses, mRNA, and gene-editing technologies. Different types of cells may be isolated from each patient, equipment may be different, or modular pieces of equipment may come together in a different order. There are also dozens of manual processing steps that take many days to complete.

A platform process offers a reliable standard process from beginning to end across different products in the same modality, which leads to similar process steps, methodologies, equipment, and testing. Where the variation lies—to pivot from one indication to another—is at the transgene level. The industry is moving in this direction, with fully three-quarters of respondents having a platform now or planning to have one in less than three years (see Figure 5).

Companies working toward a platform process may opt to tailor their process to an available "process-in-a-box" solution or optimize it to best fit the available modular technology in the market.

Standardize

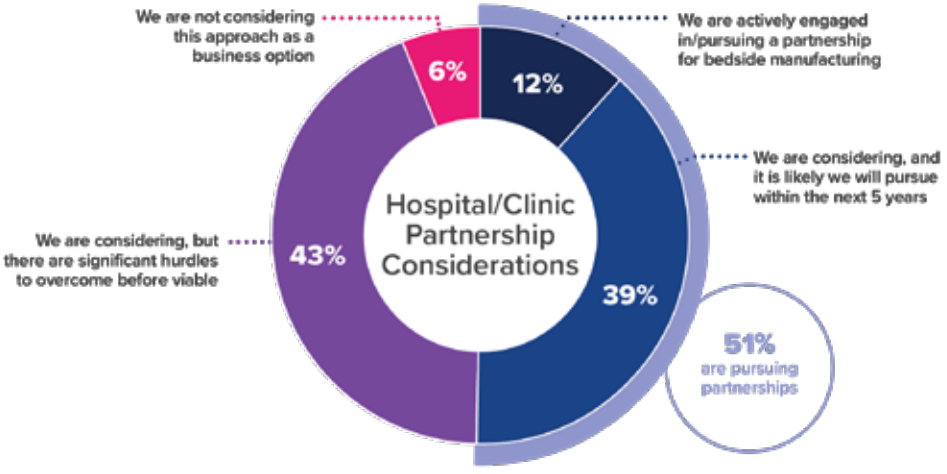
Standardization allows companies to take advantage of platform processing, which could save time and money by streamlining commissioning, validation, and regulatory approval; simplifying operator training through cross-training and interoperability; reducing labor needs and costs; and diminishing unexpected manufacturing changes during technology transfer.

A standardized, platform-based facility will give companies the flexibility to support multiple product profiles in one facility, using the same equipment and materials. It also can be customized to adapt to other variables, such as geographical location or scalability. It uses the same facility, equipment, and materials for multiple product profiles. Process-in-a-box equipment enables faster deployment and gives patients faster access to cell therapies.

GETTING READY FOR POINT-OF-CARE MANUFACTURING

The downsides of the centralized manufacturing model revolve around complex logistics. Delicate materials often need to be moved from a patient at the clinic to an apheresis center, then to a manufacturing facility for processing, and then be transported back to the patient for treatment. In addition, there are rigorous in-process control and release testing protocols to ensure product quality and safety before it can go back to the patient. The effectiveness of a cell therapy depends on a cold chain that is vulnerable

Figure 6: Autologous cell therapy makers were surveyed on whether they are considering partnering with a hospital or clinic to provide bedside cell therapies.



at each of these steps. Transportation introduces significant risk to the endeavor—one delay could ruin a batch.

Point-of-care manufacturing removes many of these steps, thus lowering risk and enhancing patient access while strengthening the chain of identity and chain of custody and reducing the need for a cold chain to maintain cell viability. An automated, closed-platform process enables point-of-care manufacturing and does so in less-expensive, lower-classified spaces with minimal interventions. Companies can reduce staffing numbers and training timelines, meaning operator expenses are not multiplied as the process is scaled out.

There are currently aseptic processing suites within a few major university-based medical centers, and, with time, this option could become more widely accessible. An automated process can be industrialized and potentially integrated into a process-in-a-box because it is more predictable and has better definition and less variability. Automated equipment lends itself to the promise of inline analytics and data collection to monitor quality and provide feedback to improve the process.

The allure of a platform process, and the point-of-care manufacturing it allows, is especially evident for makers of autologous cell therapies. Almost all those surveyed (94%) indicated they were either engaged or open to considering a partnership with a hospital or clinic to provide bedside cell therapies (see Figure 6).

If a platform process is available, the process will travel well and can be done in a smaller current GMP environment or even within or close to a medical center. This point-of-care manufacturing and delivery improves patient accessibility.

CONCLUSION

If our industry is going to fulfill the promise of cell therapies, significant challenges need to be addressed. Using the collective experience of hundreds of cell therapy industry experts working at innovative companies, we have identified design strategies to inform and support improved patient access to curative therapies. Designing to include process closure, using standardized process platforms, and embracing Pharma 4.0™ initiatives will have the synergistic effect of driving down costs and speeding up delivery of these life-saving therapies.

Cell therapy manufacturing is a nascent sector of the pharmaceutical industry. Although we are still a few years away from an ideal facility that embraces these technologies, cell therapy manufacturers are moving as fast as they can to apply pioneering technologies to benefit patient populations that, in many cases, are critically ill.

References

1. Novartis. "Novartis Five-Year Kymriah® Data Show Durable Remission and Long-Term Survival Maintained in Children and Young Adults with Advanced B-Cell ALL." 12 June 2022. www.novartis.com/news/media-releases/novartis-five-year-kymriah-data-show-durable-remission-and-long-term-survival-maintained-children-and-young-adults-advanced-b-cell-all
2. Dutton, G. "Breakthrough Therapies are Breaking Patients' Banks. Key Changes Could Improve Access, Experts Say." Leaps.org. 27 February 2023. https://leaps.org/affordable-health-care/particle-1
3. Robbins, R. and S. Nolen. "A Dilemma for Governments: How to Pay for Million-Dollar Therapies." *New York Times*. Published 24 January 2023. www.nytimes.com/2023/01/24/health/gene-therapies-cost-zolgensma.html
4. CRB. *Horizons: 2022 Life Sciences*. Published 27 January 2022. https://go.crbgroup.com/2022-horizons-life-sciences-report

About the authors

Allan Bream is a Senior Fellow of Biopharmaceutical Process with more than 35 years of engineering and biomanufacturing experience. Allan's expertise includes large-scale bacterial fermentation, mammalian cell culture, vaccines, cell and gene therapy, downstream processing, protein purification, biosafety and regulatory, and current GMP facility design, operations, and assessment. Allan joined ISPE in 1995.

Jan Bondoc, AIA, is a Process Architect with CRB with 10 years of experience focused on designing current GMP facilities for the biotechnology and pharmaceutical industries. Jan's experience includes domestic and international current GMP regulatory interpretations. Jan combines knowledge of architecture, building codes, process, and regulation, providing a strong basis for integrated facility design.

INDEX

CLASSIFIEDS

ARCHITECTURE/ENGINEERING/ CONSTRUCTION

EI Associates
8 Ridgedale Avenue
Cedar Knolls, NJ 07927
+1 973-775-7777
www.eiassociates.com

Fluor Corporation
100 Fluor Daniel Drive
Greenville, SC 29607
+1 864-281-4400
www.fluor.com

IPS-Integrated Project Services, LLC
721 Arbor Way
Suite 100
Blue Bell, PA 19422
+1 888-366-7660
www.ipsdb.com

ENGINEERING & DESIGN SERVICES

Unispace Life Sciences
NSC Campus Mahon
Mahon
Cork, Ireland
+353 21-230-7120
www.biopharmaengineering.com

INFORMATION TECHNOLOGY

COPA-DATA
Karolingerstrasse 7b
Salzburg, Austria 5020
+43 662-43-1002-0
www.copadata.com

INSTRUMENTATION

Endress & Hauser Group Service AG
Kaegenstrasse 2
4153 Reinach BL, Switzerland
+41 61-715-7700
www.endress.com

PROCESSING & MANUFACTURING

MFG Tray Company (Molded Fiber Glass Tray)
6175 US Highway 6
Linesville, PA 16424
+1 814-683-4500
www.endress.com

SOFTWARE SIMULATION & PROCESSING SYSTEMS

Intelligen, Inc.
2326 Morse Avenue
Scotch Plains, NJ 07076
+1 908-654-0088
www.intelligen.com

WATER TREATMENT & PURIFICATION

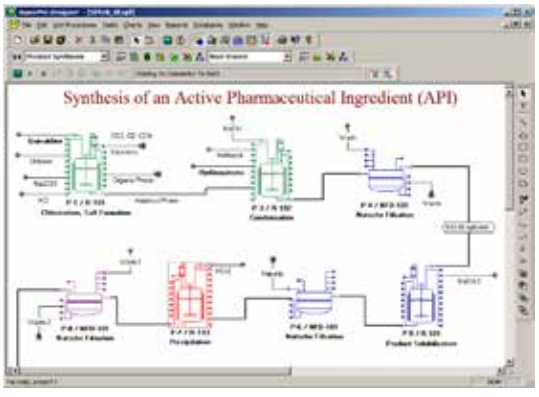
Elettracqua Srl
Via Adamoli 513
16165 Genoa, Italy
+39 010-8300014
www.elettracqua.com

PLEASE SEE THE ADS FOR EACH OF OUR ADVERTISERS IN THIS ISSUE.

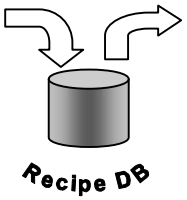
Intelligen Suite®

The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Multi-Product Facilities

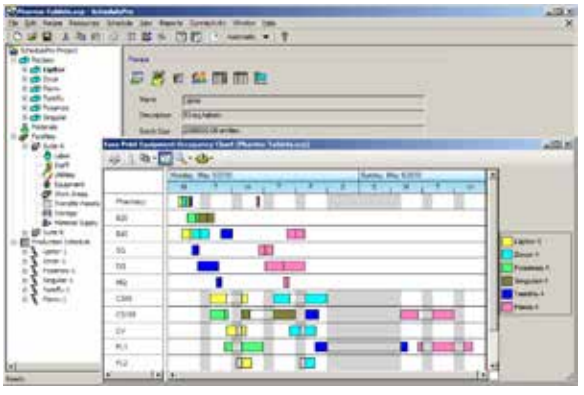
SuperPro®



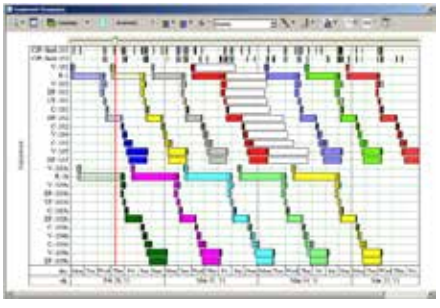
Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes



SchedulePro®

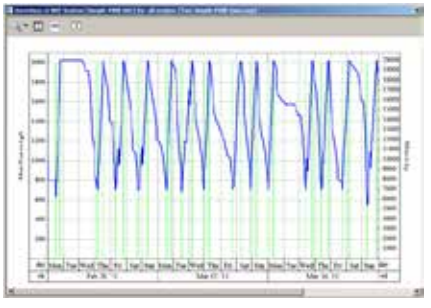


Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



Easy production tracking, conflict resolution and rescheduling

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



Managing inventories for input, intermediate, and output materials

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 500 companies and 900 universities around the globe (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

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.

Visit our website to download detailed product literature and functional evaluation versions of our tools

INTELLIGEN, INC. • 2326 Morse Avenue • Scotch Plains, NJ 07076 • USA
Tel: (908) 654-0088 • Fax: (908) 654-3866
Email: info@intelligen.com • Website: www.intelligen.com
Intelligen also has offices in Europe and representatives in countries around the world

ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

DESIGN AND CONSTRUCTION OF PURIFIED WATER PACKAGES ♦ DOUBLE PASS REVERSE OSMOSIS ♦ R.O. + ELECTRODEIONIZATION HOT WATER SANITIZABLE ♦ ULTRAFILTRATION ♦ MULTIPLE - EFFECT DISTILLATION UNITS ♦ PURE STEAM GENERATORS ♦ STORAGE AND DISTRIBUTION LOOP ♦ COMPLETE TURNKEY PROJECTS ♦ VALIDATIONS IQ, OQ

www.elettracqua.com