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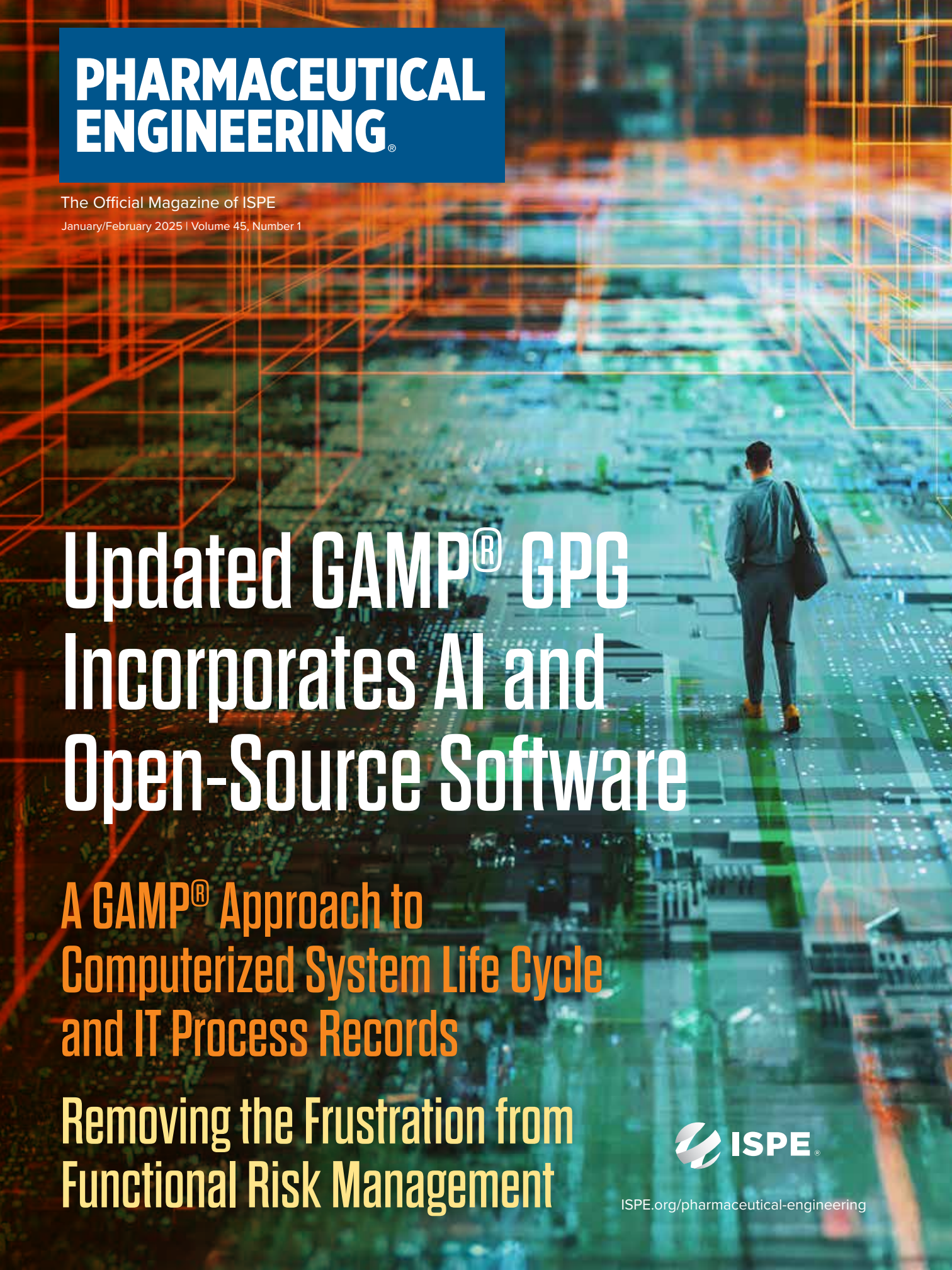

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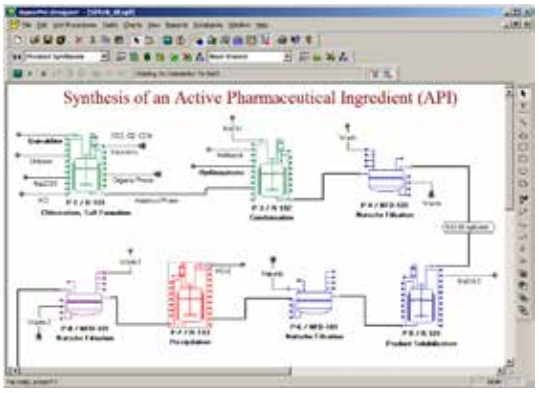

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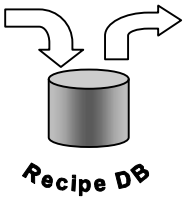

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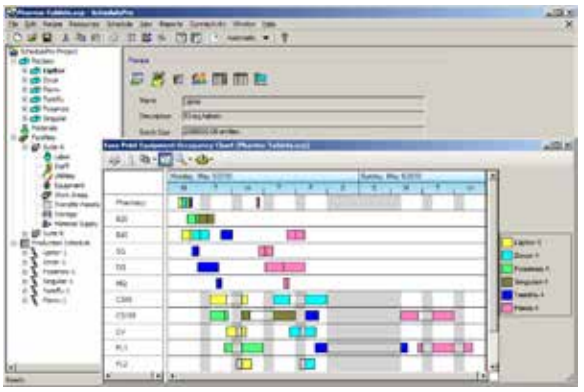

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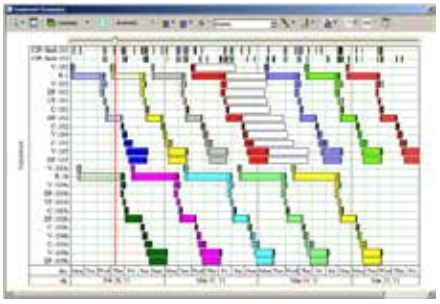

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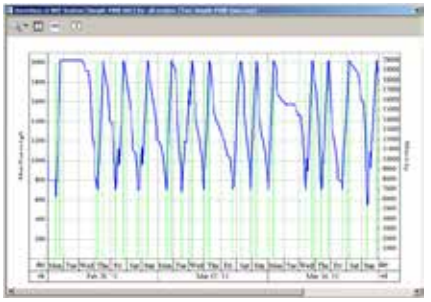

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By Jeffrey A. Biskup, PE

Jeffrey A. Biskup, PE

Celebrating 45 Years of Innovation

For nearly half a century, ISPE has served as a resource for the industry. With a global footprint that includes 22,000 members representing 120 countries, we continue to provide guidance to address pressing challenges within the industry.

ISPE is growing. We now have 22 Communities of Practice (CoPs), with the recent additions of Artificial Intelligence (AI) and Sustainability CoPs. Our global presence is expanding as well, with 40 Affiliates and Chapters.

We are proud of our history and always want to engage with pharmaceutical engineers who have been with us from the start. As we look ahead to 2025, we also want to broaden our collective perspective to ensure we're supporting all aspects of the pharmaceutical industry. We will advance our vision of shaping the future of the global pharmaceutical industry by providing solutions to complex challenges through manufacturing and supply chain innovation, member and workforce development, and technical, regulatory, and quality leadership.

In 2025, we will stay true to our mission: ISPE is the global industry leader in connecting pharmaceutical knowledge to deliver manufacturing innovation, supply chain resilience, operational excellence, and regulatory insights to advance industry efforts to develop, manufacture, and reliably deliver quality medicines to patients. This entails a more expansive approach. It involves a heavy focus on engagement with regulators and those in quality assurance.

FOCUS ON INNOVATION

The industry shows persistent promise and, at the same time, has complex challenges to address on the road ahead. These include manufacturing and supply chain innovation, member and workforce development, and technical, regulatory, and quality leadership.

We have made strides in providing GAMP-related guidance to the industry and will extend our commitment to do so in 2025. We are grateful to our dedicated "GAMPers" for their many years of service as dedicated volunteers and are happy to celebrate the 25th anniversary of GAMP Americas.

In 2024, we released the *ISPE GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data – Good eClinical Practice (Second Edition)*. As we look ahead to 2025, we have already begun to pursue revisions of at least three ISPE GAMP Good Practice Guides to ensure they are as up to date as possible. We were also proud to announce our ISPE AI® initiative in the second half of 2024. We will endeavor to support companies and the industry in the responsible adoption of AI as more applications are identified and case studies are tested for this rapidly evolving technology. Additionally, ISPE was recognized with an APEX Award of Excellence in Writing for "ChatGPT, BARD, and Other Large Language Models Meet Regulated Pharma," published in *Pharmaceutical Engineering*® in 2024. This marks the fifth consecutive year *Pharmaceutical Engineering*® has received an APEX Award.

In 2025, we look forward to releasing a highly anticipated ISPE GAMP® Good Practice Guide on AI. We will also advance our recently launched AI CoP. Our conference attendees will continue to benefit from educational sessions on AI. Our 2024 ISPE

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Annual Meeting & Expo included 16 presentations on AI. We'll provide even more AI- and Pharma 4.0™–related content in 2025 at the upcoming 2025 ISPE Facilities of the Future Conference and 2025 ISPE Biotechnology Conference. In the second half of 2024, we launched three AI-focused webinars, all part of a six-part series titled, "AI/ML in Regulated (GxP) Life Sciences Sectors."

Sustainability is another priority area for which ISPE is providing additional support to the industry. We launched a new Sustainability CoP in late 2024. We will continue to grow this CoP and plan to release an ISPE guide on sustainability in 2025. Additionally, we will accelerate our strides in Pharma 4.0™ to support the industry's persistent pursuit of digital transformation as new technologies proliferate.

RECENT ISPE ACCOMPLISHMENTS

I'd like to take a moment to highlight an especially significant ISPE accomplishment that has positively impacted the industry: the release of the updated *ISPE Baseline Guide Vol 6: Biopharmaceutical Manufacturing Facilities (Third Edition)* in late 2023. The first edition of this ISPE Baseline Guide was released in 2004. At that time, biopharmaceutical practitioners were aware of the wide variety of processes available, and with parallel improvements in analytical methods, they had evolved a better understanding of the cause-and-effect relationship between process variables and product quality. However, the technology was still advancing rapidly, and the industry was working hard to move forward. For example, single-use technology and segregation of open processes in isolators were not yet widely adopted technological advances in 2004. The industry still had a lot to learn, and companies had a lot to learn about adapting to new biopharma technology.

Fast forward to 2023: The biotech industry had matured significantly, and the latest revision of this ISPE Baseline Guide has been updated substantially. I highly recommend investing in this valuable resource if you haven't done so already. The ISPE guide team that wrote the 2023 edition has done a great job.

We anticipate a successful year ahead: celebrating our successes, honoring our commitment, and shaping the future of the pharmaceutical industry. We will continue to expand ISPE's service to the industry by connecting pharmaceutical knowledge to help organizations deliver manufacturing innovation, supply chain resilience, operational excellence, and regulatory insights to support the development, manufacturing, and reliable delivery of quality medicines to patients. Thank you for your support. We look forward to sharing a successful year together.

Jeffrey A. Biskup, PE, is a Co-Founder of Clark, Richardson and Biskup Consulting Engineers Inc. (CRB) where he serves as CEO and Executive Chairman of the Board.

By Rebecca Roscher


Rebecca Roscher

THE CHALLENGE TO CHANGE: SUCCEEDING PROFESSIONALLY

For decades, success within the pharmaceutical sector was governed and constituted by linear career paths. A linear path, though predictable, may disregard an individual's personal drivers and goals. Professional success should not only be defined through the height of your ladder position, but also by the alignment of your work to personal interests.

Aligning work to your personal interests provides a sense of purpose, as displayed by the principle of ikigai.

Early-in-career professionals are prone to falling into the trap of squeezing themselves into a predefined model of achievement. A linear career path poses the risk that these professionals may feel trapped and dissatisfied. Aligning work to your personal interests instead provides a sense of purpose, as displayed by the principle of ikigai. This Japanese concept celebrates the intersection of what you love and what you're good at, but also what the world needs and what you can be paid for.

What does the pharmaceutical world need now and in the coming years? In this time of volatility, uncertainty, complexity, and ambiguity (VUCA), technical standards can rise at any given time through advancements in automation, machine learning, and artificial intelligence. Further, we have seen how war, natural catastrophes, and pandemics can alter resource availability and our complete way of working, impacting job safety in general.

This VUCA world demands one major thing from employees: a quick adaptability to change, which makes a broad skill set highly valuable. This is why organizations started emphasizing opportunities for lateral career movements. But how can we bridge the demand for lateral skills with the pursuit of professional success when society only measures success by vertical movement? How do we prevent the impression of career stagnation?

First, we need to gain a relaxed mindset that embraces change. Second, we ought to redefine our perception of career to include fluidity. This will allow for the necessary flexibility of growth. Unlike career development, which suggests a fixed path and endpoint like product development, professional growth implies no predetermined direction or limit. It carries a sense of nurturing, allowing the possibility of aligning personal and professional priorities.

HOW TO CHANGE AND GROW SUCCESSFULLY

Know Your Priorities and Drivers

To build a stable core for the professional life, self-awareness and reflection are key. As elaborated in *The Palgrave Handbook of Fulfillment, Wellness, and Personal Growth at Work*, regularly assessing your current drivers empowers you to make decisions more easily and with a deeper sense of purpose [1]. Intuitive career decisions invite you to pursue what feels right in the moment, which leads to more fulfilling career decisions and a clearer understanding of your authentic self and goals, helping you be more confident in yourself and better prepared for change.

Visualize SMART Goals

Define your goals based on your interests and drivers, then visualize them via a vision board, an Excel file, or a Post-it note. Think of your goals as progression parameters and make them SMART: Specific (somewhat), Measurable, Achievable (with your own efforts), Relevant (to you personally), and Time-bound (transient). With SMART goals, you're in a better position to track work goals, such as taking on new assignments to polish skills you want to hone. Before or during big changes, you can create your safety net by assessing how you can enable your goal pursuit even after making a change. It will let you focus on avoiding stagnation in future situations instead of mourning old ways.

Follow Your Intuition and Make Interest-Based Decisions

Professional stability is not often felt based on how secure your job is, but rather when you feel your work has purpose and are satisfied

with your tasks and responsibilities. We flourish when we follow our passions. If you follow your interests when choosing a new opportunity, even despite high risks, it will never be a wrong decision. Interests might shift, just as priorities do over time, but that is not a problem if we allow ourselves to be flexible. Aligning your professional and personal interests will let you enjoy work more and make you resilient to the stress of frequent change.

Reduce the Tension of Getting it Right Immediately

Just like mobile phone software and apps that receive regular updates, we can continuously improve through trial and error until we succeed. If the current version of yourself didn't get it right the first time, you will learn from this experience. Adapt your approach so that the next version of yourself might succeed.

Learn New Things and Establish a Broad Talent Portfolio

Focusing on professional growth through lifelong learning builds a diversified and evolving talent portfolio, which is crucial to thrive in today's job market. Exposure to new topics and continuously acquiring new skills enhances resilience and adaptability, as well as employability, during VUCA times. Gradually reduce the unknowns step by step; this will empower you to handle future uncertainties and manage significant changes.

REDEFINING SUCCESS AND EMBRACING CHANGE

The shift toward professional growth over career development reflects a broader redefinition of success. Modern professionals are moving away from rigid career paths and are embracing flexible, interest-driven approaches. By focusing on growth, individuals can adapt to the fast-changing job market and pursue careers aligned with their evolving priorities without fear.

Professional growth leads to a more fulfilling, adaptable career, where success is defined by personal satisfaction, continuous learning, and alignment with core values. This approach helps us achieve career success alongside a greater sense of purpose and wellbeing.

Winston Churchill said, "To improve is to change; to be perfect is to change often."

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1. Marques, J. *The Palgrave Handbook of Fulfillment, Wellness, and Personal Growth at Work*. Palgrave Macmillan Cham, 2023. https://doi.org/10.1007/978-3-031-35494-6

Rebecca Roscher is a Project Manager for Bayer AG's Supply Center Grenzach in Germany. She is a trained scientist in molecular medicine, specializing in the research and development of immune therapies. She has a strong passion for cell and gene therapies and project management. Her interest in pharmaceutical engineering was sparked after joining ISPE in 2020. She is a member of seven ISPE committees, served as the representative for Emerging Leaders at Pharma 4.0 last year, and is an ex-officio member of the 2024-2025 ISPE International Board of Directors.


Lou Schmukler

CHARACTER IS DESTINY

Mahatma Gandhi, Winston Churchill, and Golda Meir were some of history's greatest leaders. One thing they all had in common was that they were leaders of incredible personal character. General Norman Schwarzkopf said, "Leadership is a potent combination of strategy and character. But if you must be without one, be without the strategy."

In the inaugural edition of this column published in the November/December issue, I shared five key principles of effective leadership. The first of the five was having the highest ethics and integrity. I placed this principle first because I believe it is the most essential quality of successful leadership. To further examine this principle, I'd like to consider it under the broader umbrella concept of character. Character extends beyond ethics and integrity. We'll look to answer a few key questions about leadership character to assist our understanding of the concept: How is leadership character defined? Why does it matter? And how can it be measured and developed?

We can break leadership down into three main components: competency, commitment, and character. Competency refers to knowledge and skills. Commitment means a willingness to do the hard work. Character is somewhat more difficult to define and measure. It can be thought of as a combination of values, traits, and virtues that shape how a leader goes about their job. Values are beliefs about what is important and worthwhile. Traits are habitual patterns of thought, behavior, and emotion. VVirtues are a concept that is less understood.

The ancient Greek philosophers defined virtues as courage, moderation, justice, and wisdom. With a few additions, such as accountability, humility, etc., I think this definition still stands today. Character is doing the right thing, for the right reasons, and with the right mindset. It is central to being able to effectively lead people and organizations. So, although character can seem subjective and difficult to comprehend, it can be reliably defined, developed, and measured.

> When leaders are faced with especially tough situations, their character is revealed and becomes most critical. Martin Luther King, Jr., said, "The ultimate measure of a man is not where he stands in moments of convenience and comfort, but where he stands at times of challenge and controversy."

Many organizations do not devote adequate attention to leadership character. This is a significant missed opportunity. Character matters because it can affect the quality of leadership and the outcome of a leader's actions. Leaders can marginalize it, not realizing that it is foundational to other important leadership attributes or that it can have a major impact on the organization's culture. And there is certainly a correlation between leadership character and organizational performance. Research has shown that leaders and organizations with high leadership character scores deliver five times the return on assets than those that score lower.

A leader's character shapes how they interact with their environment, and most importantly, it shapes their decision-making process. Every day, leaders make decisions, large and small, consciously or unconsciously, such as between speed or quality, long-term vs. short-term results, or whether to terminate an employee. These decisions can have a significant impact, both internally and externally.

When leaders are faced with especially tough situations, their character is revealed and becomes most critical. Martin Luther King, Jr., said, "The ultimate measure of a man is not where he stands in moments of convenience and comfort, but where he stands at times of challenge and controversy." These "moments of truth" can differentiate a great leader from the mediocre and shape a leader's legacy.

We find various organizations investing much more in competency development than character growth. Leaders can be exceedingly competent and achieve great operational success, yet still lack character. This often leads to organizations with strong results but an unhealthy culture and poor employee engagement. Character, therefore, can be considered as important as competence when it comes to evaluating leadership potential.

Organizations need to be more intentional when it comes to leadership character development. Mere posters on a wall and clever catchphrases are insufficient. We know that what management focuses on gets done and what is ignored is dismissed. To place the right emphasis on leadership character development, it needs to be a regular part of the conversation. It should be included in position profiles and assessments. Making it a criterion for promotions, succession planning and recruitment is also important. It should be included as part of coaching and mentoring initiatives and reinforced through company training programs. Validated assessment tools can help measure progress.

Over the past decade, we've come a long way in our understanding of leadership character. A leader's character can now be assessed and developed as easily as leadership competencies. Strong leaders possess more than just leadership competencies; they also possess leadership character. Character enables leaders to navigate change and drive better alignment, teamwork, productivity, creativity, and overall organizational effectiveness.

Lack of character can have a significant negative impact on the organization and result in leader derailment. As we progress in our career, and our responsibilities grow, our character will be tested at new and higher levels of intensity. So, character development needs to be an ongoing process.

In conclusion, I would submit that leadership character can and should be appropriately viewed from the perspective of a strategic and competitive advantage for the organization.

Lou Schmukler served as Executive Vice President and President of Global Product Development and Supply at Bristol Myers Squibb until his retirement. His pharmaceutical industry career spanned over 40 years. He holds a BS from Temple School of Pharmacy and an MA from Webster University. He joined ISPE in 1993.

By Vivien Santillan


Vivien Santillan

EMPOWERING WOMEN IN PHARMA FOR COLLABORATION AND GROWTH

In the ever-evolving landscape of the pharmaceutical industry, the Women in Pharma® Steering Committee has taken significant steps to foster collaboration, share insights, and strengthen community engagement among the ISPE community. Over the past year, our commitment to these initiatives has opened doors for Women in Pharma Affiliate and Chapter leaders to connect, exchange best practices, and collectively enhance the Women in Pharma program.

BUILDING GLOBAL CONNECTIONS

Recognizing the value of a diverse and interconnected community, the Women in Pharma Steering Committee initiated a global engagement strategy. This strategy includes a platform for Women in Pharma leaders from Affiliates and Chapters to share their events, insights, and plans, which bridges geographic boundaries for a robust support network. This collaborative approach not only strengthens our initiatives, but also enriches the experiences of our members. Open forum sessions were organized, inviting leaders to discuss how we can further improve the Women in Pharma program, ensuring its relevance to the ISPE community and the pharmaceutical industry in general. This dialogue has sparked innovative ideas and renewed enthusiasm for our shared mission.

GOALS AND ASPIRATIONS: A VISION FOR THE FUTURE

Mentorship Programs

The success of our mentorship program has been a highlight of our initiatives. As we prepare for its third run in 2025, we are committed to introducing new programming and improvements that enhance engagement and support for our members. By fostering mentorship, we empower our members—whether they are students, Emerging Leaders, or professionals—to navigate their careers, continue to inspire, and reach their full potential.

Webinars

To further develop our members and prepare the workforce of the future, we will continue to align with the ISPE mission to connect pharmaceutical knowledge to deliver manufacturing and supply chain innovation, operational excellence, and regulatory insights to enhance industry efforts to develop, manufacture, and reliably deliver quality medicines to patients. ISPE webinars will serve as valuable learning opportunities, providing insights into industry trends, professional and personal development, and leadership strategies.

Engagement in Conferences

Active participation in conferences is essential for building connections and showcasing our initiatives. The Women in Pharma Steering Committee aims to ensure our presence at every conference, organizing dedicated sessions that highlight our work and promote networking among attendees.

Social Impact Initiatives

We believe that our commitment to social impact is a cornerstone of our mission. By focusing on initiatives that create meaningful change within our communities, we not only uplift Women in Pharma, but also contribute positively to society. Our advocacy for diversity, equity, and inclusion (DEI) will serve as a key focus as we aim to foster an environment that is aware, compliant with strategic initiatives, integrated, and sustainable. By promoting DEI principles, we can create a workplace that is inclusive and supportive for all.

The Women in Pharma program will continue to drive meaningful change and create a supportive network for women and allies in the pharmaceutical industry. Through our initiatives, we strive to empower members, advocate for social impact, and champion DEI principles. As we move forward, we invite all stakeholders to join us in this journey toward a more inclusive and equitable future.

Together, we can make a difference—one connection, one mentorship, and one initiative at a time—as we shape the future of pharma.

Vivien E. Santillan is Regional Director for Asia and Novatek International and the 2024–2025 Chair of the ISPE Women in Pharma International Steering Committee. She has been a member of ISPE since 2012.

Mike Martin Named President and CEO of ISPE, ISPE Foundation

By Katie LeChase

Mike Martin assumed his new role as President and CEO of ISPE and the ISPE Foundation in January.


Mike Martin

The announcement was made in October. "We are pleased to announce Mike Martin will be joining ISPE and the ISPE Foundation as the new President and CEO," said Jeffrey Biskup, Chair of the ISPE International Board of Directors and Executive Chairman of the Board for CRB. "ISPE extends its sincere gratitude to Michael Rutherford for his outstanding leadership and commitment during his tenure as Interim President and CEO. His guidance and dedication have been instrumental in ensuring ISPE's continued success through this transition."

Martin has had a distinguished career spanning more than 35 years in the pharmaceutical industry.

Martin has had a distinguished career spanning more than 35 years in the pharmaceutical industry. Most of his career was with a large global pharmaceutical company, where he held leadership positions in engineering, operations, and project management across diverse global settings. Martin most recently served as the CEO of an engineering consulting company. His extensive experience includes leading large-scale capital projects in the US, Puerto Rico, China, and Ireland. He holds a bachelor's degree in mechanical engineering and a master's degree in business administration, as well as a professional engineering license.

"Mike Martin has successfully led diverse teams in various settings. He has demonstrated his ability to integrate into different cultures and inspire teams to achieve ambitious goals," said Michael Rutherford.

As a seasoned professional, Martin's experience spans a variety of pharmaceutical manufacturing operations, including dry product, aseptic, API, and delivery device manufacturing. He has led engineering, operational, and large-project organizations across these sectors. Martin has been a long-standing member of ISPE. Prior to assuming the role of President and CEO for ISPE and the ISPE Foundation, he served on both the ISPE International Board of Directors and the ISPE Foundation Board.

Katie LeChase, ISPE, Director of Communications, ISPE

Updated GAMP® GPG Incorporates AI and Open-Source Software

By Petch Ashida Druar, Martin Heitmann, Frank Henrichmann, Brandi Stockton, and Lorrie Vuolo-Schuessler

The landscape of clinical trials has been transformed in a post-pandemic world. The first edition of the *ISPE GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data – Good eClinical Practice* was issued in 2017. In July 2024, ISPE released the second edition [1] which addresses managing the complexities associated with an uptick in decentralized clinical trials, the benefits and challenges of using open-source software, the use of data science and AI in clinical trials, data privacy, and data processing.

The conduct of clinical trials and their support by technology solutions has dramatically changed since the first publication of the Guide. The COVID-19 pandemic forced sponsors to rapidly develop solutions so that clinical trials could be conducted during lockdown, which led to the significant adoption and advancement of decentralized trials. This paradigm shift required technical solutions that were patient-friendly, easy to use, fit for purpose, and compliant.

The pandemic also pushed the analysis of real-world data (e.g., from electronic health records) in attempts to find treatment approaches from data collected outside of clinical trials. Both approaches require handling huge amounts of data, necessitating using tools typically associated with processing big data.

In parallel, significant advancements in artificial intelligence (AI) and machine learning (ML) have enabled new approaches for clinical trials, from protocol design to clinical trial closure. This updated guide reflects the content and concepts published in the *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* [2]. It was time for ISPE to update this key guidance document to reflect technological progress and regulatory advances.

The overall approach, framework, and key concepts as presented in the first edition remain unchanged. However, the second edition advances these concepts to continue promotion of patient safety and data integrity in clinical trials in the post-pandemic world. This is done by facilitating and encouraging the achievement of computerized systems that are effective, reliable, and of high quality. This article provides an overview of the Guide's update and discusses a selection of four major topics related to the innovations in the second edition.

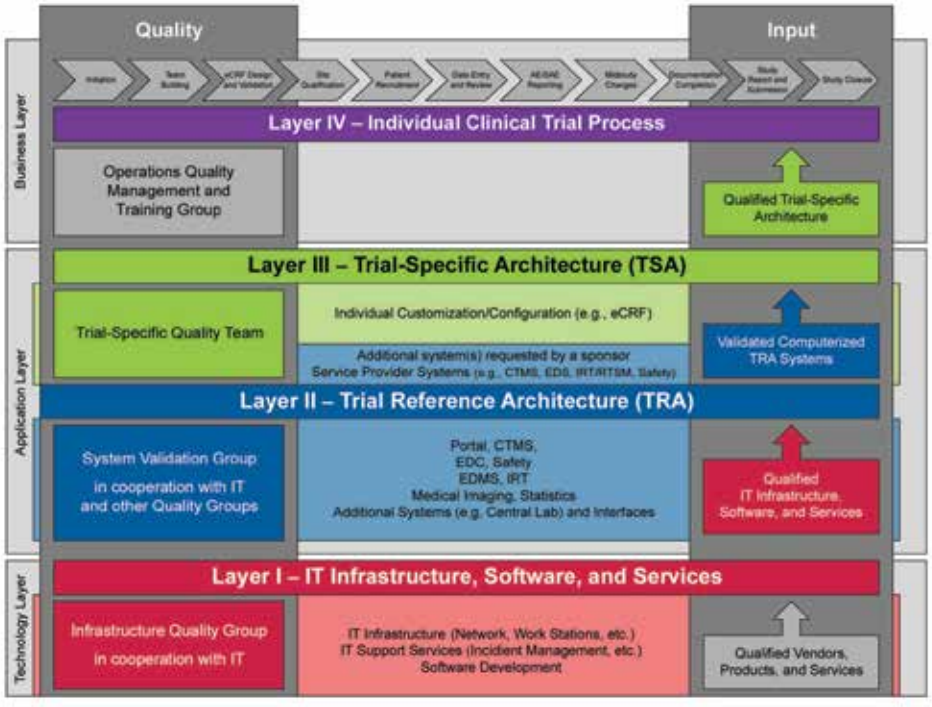
BACKGROUND AND DRIVERS

In recent years, a transition from the traditional, site-centric model to a hybrid or participant-centric decentralized model has become more prevalent. This transition was supercharged by the COVID-19 pandemic. However, the transition to more decentralized models started even earlier. The aim was to reduce cost, enhance data accuracy, improve participant access and engagement, overcome geographic barriers, and promote diversity.

Today, virtual or decentralized models have gained traction as clinical trial computerized system applications enable remote data collection and virtual monitoring. Regulators have reacted to this and issued guidance for decentralized models, such as the US Food and Drug Administration's (FDA) guidance on "Conducting Clinical Trials with Decentralized Elements" [3].

Decentralized clinical trials (DCTs) led to an increase in the development and usage of wearables and sensors within clinical trials. These technologies produce vast amounts of data, as they are continuously monitoring parameters and recording data that are important for a clinical trial. The management, evaluation, and analysis of this data requires approaches and tools by which clinical trial teams can extract insights from large amounts of data. As such, manual review, control, and assessment by humans is becoming infeasible. Still, these approaches need to be fit for the purpose. Therefore, data management in clinical trials has evolved into data science and is now adopting advanced approaches including the use of AI methods, ML in particular.

Figure 1: Overview of clinical project layers [1].



Similar amounts of data from various sources in the real-world context are evaluated by researchers to gain new insights or leads and to support controlled clinical trials. The quality of such real-world data, their management, and further analysis is of key importance to allow the generation of real-world evidence. The impact of biased data and inappropriate methodology proposes a significant risk to the safety of patients. This is highlighted by the COVID-19 hydroxychloroquine study published in *The Lancet* that had to be retracted because the findings were based on electronic health record (EHR) data from inconsistent sources, compromising the overall quality of the combined data set [4–5].

All real-world data and data collected, used, and analyzed in clinical trials originate from humans. This data is typically of a highly sensitive nature because it is concerned with medical conditions, treatments, and lifestyles. Therefore, the protection of data privacy is paramount when conducting clinical trials using real-world evidence and in the management of associated real-world data.

The outsourcing of clinical trials and supporting technology has progressed further since the first edition's release. Almost all sponsors and clinical service providers routinely use the cloud-based Software-as-a-Service (SaaS). The regulators have issued guidance documents, including the European Medicines Agency's (EMA) "Guideline on Computerised Systems and Electronic Data in Clinical Trials" [6].

This guidance clarified the quality expectations and roles and responsibilities in the usage of cloud service providers, such as SaaS. Additionally, it also clarified the quality expectations on clinical site operated systems that are used to generate, collect, or analyze data during a clinical trial. Furthermore, the guide needed to be aligned with the concepts and principles of *ISPE GAMP® 5 (Second Edition)* [2]. This included emphasis on critical thinking, testing of computerized systems, and guidance on outsourced IT infrastructure or systems.

GAMP guidance must stay fully aligned with current good practice to provide optimal value to the industry, avoiding guidance based on outdated technical concepts, approaches, or techniques, even if such concepts, in some cases, remain in regulatory guidance or company policies and procedures. In light of current developments as described in this article, an update of the *ISPE GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data – Good eClinical Practice* [1] was necessary.

OVERVIEW: FRAMEWORK AND NEW CONCEPTS

The updated Guide contains the same approach and key concepts, including the Clinical Project Layer Model, from the first edition (see Figure 1). It also provides the following:

- Updated overview of current regulatory guidance documents
- A high-level process overview, including the Clinical Project Layer Model
- Relevant data flows
- Required oversight activities
- Inspection readiness
- A risk-based approach for the setup of clinical systems

Each process step—from planning, conduct, and analysis to reporting—is analyzed for its potential risks to patient safety and the data integrity of the potential supporting technologies. Then an outline is formed for a potential validation approach for these technologies. The life cycle of clinical data and the associated data integrity risks are analyzed, and approaches for mitigating these risks are presented. This includes specific guidance for electronic source data, audit trails and audit trail reviews, interfaces and their validation, electronic and digital signatures, and certified copies.

The newly created appendices provide practical guidance on (1) data privacy in clinical trials, (2) the specific aspects to be considered in decentralized clinical trials (DCTs), (3) good clinical laboratory practice, (4) the use of data science and AI-enabled systems, (5) real-world data, (6) real-world evidence, and (7) the open-source software used in clinical trials. The Guide emphasizes that critical thinking should be applied through the trial, data, and system life cycle and is fully aligned with the principles and concepts of *ISPE GAMP® 5 (Second Edition)* [2].

DATA SCIENCE AND AI IN CLINICAL TRIALS

Data science disciplines, including the use of AI and ML, offer new ways to analyze data, extract information and patterns, form predictions, create recommendations, and generate content such as text and images. As such, clinical processes may be augmented with AI. AI approaches can improve efficiency of clinical trials and support success and quality of clinical trial outcomes. Especially where a high volume of data is generated, and several possible paths and choices are evaluated, classical ways of quality assurance, analysis, and assessment hit limits of efficiency and practicability. However, the statistical nature and the complexity of these approaches comes with their own risks, as is the even higher dependency on high-quality data and an understanding of representativeness of data for a given application, both for data science as well as AI approaches [7–8].

ISPE GAMP® 5 (Second Edition) appendix D11 offers a life cycle model focused on ML subsystems and the three life cycle phases of concept, project, and operation with good ML practices and operations (MLOps) [2]. These include concepts such as splitting data for training, validation, and testing purposes as well as an iterative fine-tuning approach for the final tailoring of the model, toward acceptance, release, and ongoing monitoring. In addition, the *ISPE GAMP® 5 (Second Edition)* appendix D11 elaborates on supporting processes, including risk management, data governance, and change management. This underpins the relevance and importance of data and the forward-looking perspective of careful evaluation of risks to patient safety, product quality, and data integrity.

Although *ISPE GAMP® 5 (Second Edition)* appendix D11 provides an overarching framework, this guidance needs to be interpreted and tailored for specific use cases in the clinical trial context [2]. To serve this goal, the data science and AI chapter in the *ISPE GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data – Good eClinical Practice (Second Edition)* elaborates on specific aspects that are relevant in clinical trials.

Suitability Assessments

The innovative and project nature of clinical trials requires a thorough assessment of the suitability and fitness for purpose in use of data science and AI approaches. Such assessments are performed during the concept phase of the computer system development and part of a dedicated trial.

Diligence

Clinical trial protocols require diligence, not only in terms of patient safety, but also commercial viability regarding the use of AI, ML, and data science approaches.

Patient Data

Clinical trial activities require close interaction with patient data in various process steps (e.g., recruiting, data capture, and evaluation) and potential areas of direct interaction with patients via digital health technologies. Therefore, a thorough understanding of the stakeholder ecosystem is crucial for successful use of AI in the clinical context.

Guidance Provided

Considering these aspects, the chapter on data science and AI in the new guidance document provides detailed guidance tailored to supporting clinical trial operations. In particular, the chapter provides dedicated guidance regarding the following themes:

- General definitions and an overview on regulatory standards with relevance to data science, AI, and ML concepts
- The evolution of clinical data management into clinical data science and data analytics approaches with the application of emerging technologies
- Guidance on AI-/ML-enabled systems across use cases along the clinical trials process, to provide overarching guidance on the life cycle management decisions, considerations on fitness for purpose, and importance of human–machine interaction concerning a variety of stakeholders in the clinical trial ecosystem. Example use cases illustrate potential risks to consider, risk control, and validation strategies throughout the clinical trials process

This chapter should support the safe and effective adoption of data science, AI, and ML approaches in the clinical context. These are integrated with further cross-sectoral operational guidance. In particular, this guide was developed with the focus of Good Clinical Practice (GCP) based on concepts included in *ISPE GAMP® 5 (Second Edition)* [2].

REAL-WORLD DATA AND EVIDENCE

Real-world data (RWD) and real-world evidence (RWE) have been integral in epidemiology for years, but their significance in healthcare and pharmaceutical research has surged recently. Regulatory agencies like the US FDA and the EMA now recognize the value of RWD and RWE for evaluating medical product safety and efficacy. These bodies have developed frameworks to facilitate

the incorporation of RWE in regulatory decision-making processes. Mistakes in the selection and processing of RWD have significant impact on the safety and well-being of patients, as seen in the retracted article in *The Lancet* article [4–5]. For this reason, the Good Practice Guide covers the following themes:

Key uses of RWD and RWE include:

- Clinical trials:
  - Historical control group or concurrent control group
  - Patient recruitment, site selection and feasibility assessment analyzing demographic data, treatment patterns, and healthcare utilization from RWD sources, researchers can identify sites with a sufficient patient pool for specific clinical trial criteria
  - Patient population analysis to provide insights into the characteristics and distribution of patient populations in different geographical regions

- Post-marketing:
  - Post-marketing surveillance to enable continuous monitoring of drugs and medical devices/digital health technologies after they enter the market
  - Post-market effectiveness studies to assess the effectiveness of drugs after they have been launched in the market
  - Label expansion and regulatory submissions support label expansion efforts by providing additional evidence on drug effectiveness, safety, and efficacy in broader patient populations or new indications
  - Evidence generation for the safety, efficacy, and effectiveness of interventions in diverse patient populations and real-world settings
  - Comparative effectiveness and safety studies to compare the effectiveness and safety of different drugs or treatment interventions in real-world clinical settings
  - Health technology assessment to support evaluations of pharmaceutical products providing evidence on the comparative effectiveness, safety, and cost-effectiveness
  - Treatment access and reimbursement use RWE to assess the value of therapies, make coverage decisions, and determine appropriate pricing
- Personalized medicine and biomarkers:
  - Personalized medicine and precision health (e.g., identification of patient subgroups, biomarker analyses, and treatment response assessments)
  - Identification of biomarkers that are associated with specific clinical conditions, outcomes, or treatment responses

Challenges Using RWD and RWE

Data quality and standardization

RWD is derived from various sources, such as EHRs, claims databases, patient registries, and even wearable devices. These sources often have inherent limitations, including missing data, inconsistencies, and variations in data collection practices. Ensuring data quality and achieving standardization across different sources is a significant challenge. High-quality, standardized data are crucial for generating reliable and actionable RWE.

Data privacy and security

RWD frequently contains sensitive patient information, raising concerns about privacy and security. Robust anonymization and stringent security measures are essential to protect patient privacy while leveraging RWD for research purposes. Balancing the need for data access with privacy protection is critical to maintaining public trust and complying with legal and ethical standards.

Bias and confounding

RWD can introduce biases and confounding factors that may affect the validity and reliability of research findings. Unlike randomized controlled trials, real-world studies cannot always control all variables, making it challenging to isolate the effects of the intervention being studied. Researchers must develop and apply sophisticated statistical methods to account for these biases and confounders to ensure credible RWE.

Reproducibility and transparency

For RWE to be trusted, the methods used to generate it must be transparent and reproducible. Research findings should be independently validated and reproduced to build confidence in RWD and RWE studies. This requires clear documentation of methodologies, data sources, and analytical techniques, allowing other researchers to replicate the studies and confirm the results.

Regulatory and reimbursement acceptance

Although regulatory bodies like the US FDA and EMA have recognized the value of RWD and RWE, consistent industry standards and methodologies for generating RWE are still needed. These standards are essential to ensure that RWE is acceptable for regulatory and reimbursement decision-making. Establishing clear guidelines and frameworks that provide consistency and clarity in the generation and use of RWE remains an ongoing challenge. Regulatory and reimbursement bodies must work together with industry stakeholders to develop these standards and facilitate the integration of RWE into decision-making processes.

To address these challenges the Good Practice Guide [1] provides a process for evaluating and using RWD to generate RWE, which covers:

- Determination of the intended use based on a defined research question
- Data accrual to determine the required data and their quality criteria
- Selection and assessment of data sources that can provide the required data
- Data preparation and curation, including data cleaning, usage of a common data model, and data standardization
- Management and assurance of data privacy aspects
- Data management throughout the entire data life cycle

With clinical trial computerized system applications enabling remote data collection and virtual monitoring, decentralized models have become more efficient from a technology point of view.

- Data retention requirements based on usage and applicable regulations

The detailed guidance given for each of these steps in the Guide ensures data integrity and data quality that is sufficient for the intended use of the RWE generated from RWD.

DECENTRALIZED CLINICAL TRIALS

Multiple clinical trial delivery models are used in the pharmaceutical industry. In recent years, a transition from the traditional, site-centric model to a hybrid or participant-centric decentralized model has become more prevalent. Drivers from centralized to more decentralized models include cost and limited engagement of some trial participants due to geographic and socioeconomic barriers. With clinical trial computerized system applications enabling remote data collection and virtual monitoring, decentralized models have become more efficient from a technology point of view.

According to the US FDA guidance document "Conducting Clinical Trials with Decentralized Elements," published in September 2024, DCT is defined as a clinical trial where some or all of the trial-related activities occur at locations other than traditional clinical trial sites [3]. A DCT model brings all or part of the clinical trial to the patient, such as to their home, a local healthcare facility, or a laboratory, thus reducing some of the challenges for trial participants. With a DCT, the goal is to minimize the patient burden while collecting real-time, accurate clinical trial data. While the concepts and principles of validation are consistent across GxP areas, there are key areas where additional considerations are needed to support these technologies [3].

When transitioning from traditional to a decentralized or hybrid clinical trial delivery model, the readiness of the organization's infrastructure and workforce must be considered. Integrating systems to support remote monitoring, data collection and training for the organization, clinical site staff, and patients may be needed. As with all aspects of clinical trials, regional and local regulatory compliance requirements should also be considered.

Decentralization introduces further complexities to various processes in clinical trials, including monitoring, audits, privacy and blinding, and business continuity. For instance, where the participants receive investigational medicinal products (IMPs) directly, additional focus should be placed on the expiration date. Furthermore, patient safety is a concern where access to bulk IMP may be available for the trial participant.

Reflecting on these challenges, this new chapter provides guidance regarding:

- Key prerequisites to be considered when implementing DCTs, including the business process flow, data flow, technical needs, and site feasibility
- Supplier relationship considerations and the need to ensure that contractual agreements and service level agreements are in place
- Ensuring mechanisms for data control throughout the clinical trial to maintain data integrity
- Use of digital health technologies and devices including provisioning, support, access, and safety and biohazard concerns
- Establishing fitness for intended use of a potentially complex clinical trial setup, including activities for infrastructure qualification, software development, and operational support and maintenance
- The importance of developing a dedicated training program for participants, investigators, clinical trial staff, sponsors and other parties, including training materials and the delivery method
- Considerations regarding shipment of IMPs or investigational products direct to patient or direct to site, and storage and disposal needs

GOOD CLINICAL LABORATORY PRACTICE

In clinical trials, analyzing samples from participants is crucial for proving drug effectiveness and ensuring participant safety. These samples are examined based on parameters outlined in the clinical trial protocol. Effective tracking and handling are vital to maintain data accuracy and completeness. Samples are often analyzed away from the collection site, necessitating strict control over their chain of custody, including time, environmental conditions, and transportation routes. Adequate training for staff at the collection site ensures proper sample labeling and handling, with blinding maintained throughout all stages.

Mapping the Business Process and Data Flow

To establish the necessary technical, procedural, and behavioral controls for sample and data integrity, it's essential to map out the business process and its dependencies. This involves understanding the computerized systems and responsible parties involved, from sample collection to result reporting. Particular attention should be given to system interfaces and the data life cycle (i.e., transfers, archiving) to ensure these systems are well-specified, tested, controlled, and fit for purpose. The integrity of the data must be maintained throughout the life cycle.

Risk Evaluation and Documentation

Understanding the business process and data flow allows for evaluating and documenting risks associated with the process. Key risk considerations include:

- Unavailability of source or target systems within a data flow
- Corrupted or incomplete laboratory data related to participants
- Loss of association to a participant number
- Unblinding issues depending on the trial design
- Inadequate control of third parties

Decisions should be based on risk assessments using critical thinking. Ensuring computerized systems and data transfers are specified, tested, and controlled is essential for data integrity.

Roles and Responsibilities

Samples may be analyzed by the sponsor company or third parties, including investigator sites, clinical service providers, central laboratories, hospital laboratories, or university laboratories. All partners performing sample analysis must be qualified, with responsibilities clearly defined in contracts. This clarity ensures accountability and proper management of the sample analysis process.

Regulatory Guidance

The EMA's "Guideline on Computerised Systems and Electronic Data in Clinical Trials," published in March 2023, outlines the necessary controls to ensure data integrity throughout the data life cycle [6]. This guidance addresses technical, procedural, and behavioral controls to maintain data accuracy and completeness in clinical trials.

Good Clinical Laboratory Practice

The World Health Organization's "Good Clinical Laboratory Practice (GCLP)," based on principles from Good Laboratory Practice (GLP), apply to the analysis of samples from clinical trials [9]. These principles ensure the reliability and integrity of data generated by analytical laboratories. Clinical trial samples include various assays and tests such as chemical, biological, safety laboratory samples, pharmacokinetic (PK), pharmacodynamic (PD), and biomarkers.

Quality Management Systems and Laboratory Standards

Laboratories analyzing clinical trial samples must be qualified, with all interfaces to laboratory systems validated. The EMA's "Reflection Paper for Laboratories that Perform the Analysis or Evaluation of Clinical Trial Samples," published in February 2012, details the quality system elements necessary for such laboratories, including procedures for emergency release of safety-impacting results [10].

Standard Controls and Documentation

Controls necessary to support sample analysis in clinical trials are standard requirements within quality management systems.

These include policies and procedures for environmental controls, sample labeling, storage, transport, data transfer, review and release of sample analysis, maintaining the blind, sufficient resources, appropriate training, contracts, agreements, and quality assurance. Both the *ISPE GAMP® Good Practice Guide: GxP Compliant Laboratory Computerized Systems (Second Edition)* and *ISPE GAMP® 5 (Second Edition)* provide information on ensuring computerized systems are fit for purpose. They also safeguard patient safety, product quality, and data integrity [2, 11].

The updated Good Practice Guide provides practical guidance criteria for selecting partners involved in the analysis of the samples. The requirements for the logistics and the analysis of samples are explored and a typical workflow for laboratory is outlined. Typical challenges in the implementation and validation of supporting computerized systems for this process are outlined. This includes systems such as laboratory information management systems and also addresses the data transfer between partners and the necessary retention and archiving of laboratory records. The need for clearly defined responsibilities, adequate facilities, and processes is explored in detail.

CONCLUSION

The principles of *ISPE GAMP® 5 (Second Edition)* needed to be interpreted for computerized systems used in clinical trials to provide practical guidance to validation experts that are challenged with the validation of these systems. The high degree of outsourcing, the cross-organizational usage of many of the systems, and the various regulatory aspects (including data privacy) provide unique challenges in the validation of GCP systems.

This article only outlines a few sections of the *ISPE GAMP® Good Practice Guide: Validation and Compliance of Computerized GCP Systems and Data – Good eClinical Practice (Second Edition)*. As of today, it is the most comprehensive guide on the validation of computerized systems used in the context of drug development and clinical trials available.

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A GAMP® Approach to Computerized System Life Cycle and IT Process Records

By Siôn Wyn, Arthur (Randy) Perez, PhD, Chris Reid, and Heather Watson

This article describes a practical and pragmatic approach to the management of computerized system life cycle and information technology (IT) process records. The objective is to effectively achieve and maintain compliant GxP-regulated systems that are fit for intended use, and to support patient safety, product quality, and data integrity.

INTRODUCTION AND OVERVIEW

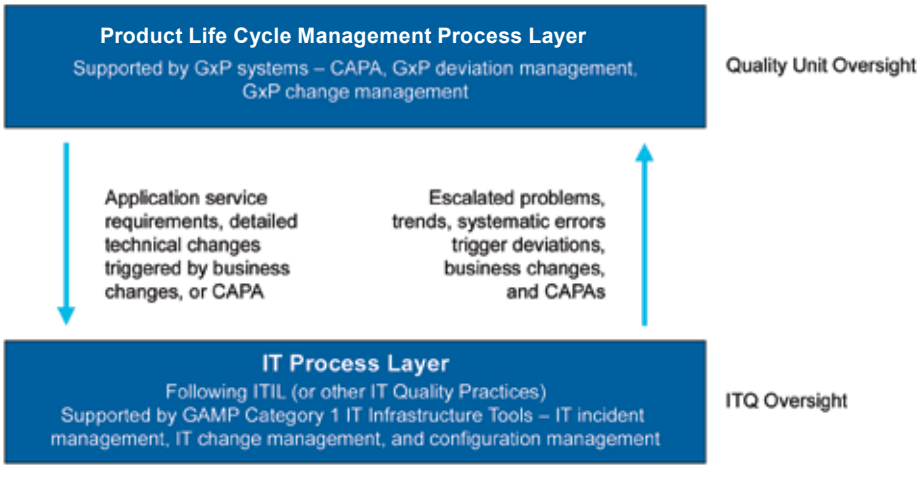
A GAMP® best practice approach is achieved by applying current good IT practice and modern software engineering techniques as well as principles supported by the effective use of commonly used standard software tools. Using practices that have been traditionally applied to GxP records, particularly paper records, can be inappropriate and unnecessary. Doing so may also potentially cause harm by:

- Increasing complexity and therefore risk
- Discouraging the use of widely used and well-understood standard tools, the application of modern methods and techniques, and effective communication between those involved
- Encouraging unnecessary duplication of information, cumbersome manual workarounds, and the development of custom, often homegrown solutions

Computerized system life cycle and IT process records managed with modern techniques and automated tools are not uncontrolled. They can be rigorously managed through access control, privilege management, security features, auditing and logging, enforced roles and responsibilities, segregation of duties, and using many other features and functions that are built into modern tools.

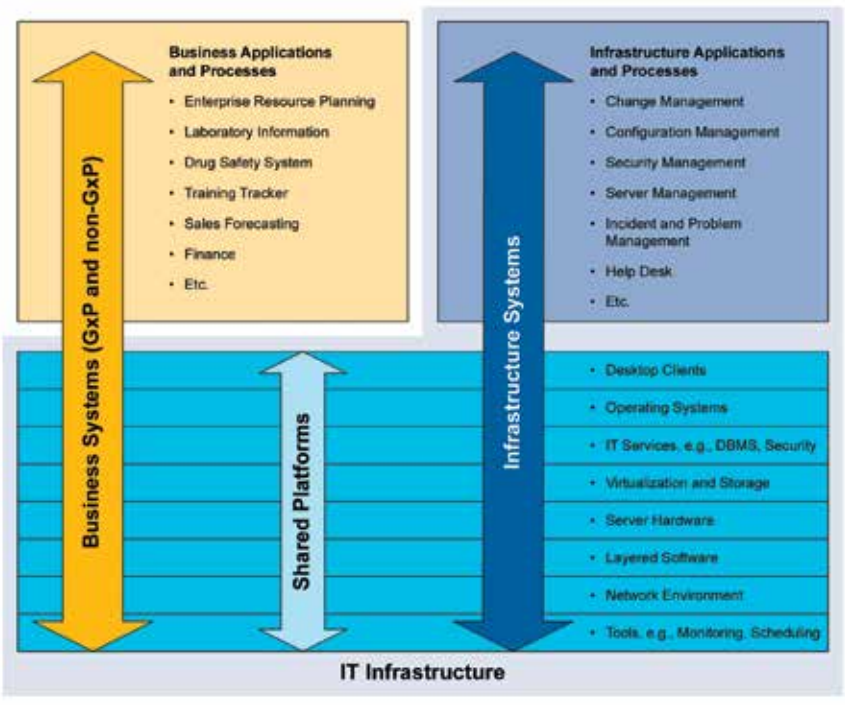
Robust, reliable, and effective GxP computerized systems that support product quality and patient safety require the application of effective modern methods and techniques that follow accepted software engineering principles and IT good practice. This includes processes such as version and configuration management,

Figure 1: Product life cycle records vs. system life cycle and IT process records [1].



CAPA: corrective and preventive

Figure 2: Relationship of IT infrastructure and processes with business systems and processes [1].



DBMS: database management system

requirements management and traceability, testing, verification and defect prevention, and release management. In a modern software and IT environment, this can only be achieved by using suitable tools.

SCOPE

GAMP® guidance makes a valuable distinction between (1) GxP records supporting the medicinal product life cycle and required by predicate rules, and (2) the information, data, and artifacts that support computerized system life cycle and IT process records (see Figure 1). This distinction, applied with critical thinking, supports an approach that is effective in reliably delivering and maintaining systems that are fit for their intended use.

Examples of computerized system life cycle records include requirements, specifications, designs, test definitions, and test results. IT process records include those supporting incident, problem, capacity, performance, change, and configuration management processes. Such records are valuable to the organization and should be securely and effectively maintained as part of the IT quality management system, but they do not directly support the GxP medicinal product life cycle.

Records supporting system life cycle management, IT, and infrastructure process are typically maintained in GAMP Category 1 systems or tools, as shown in Figure 2. A modern best practice approach to the use of such tools is described in Appendix D9 – Software Tools of *GAMP® 5 (Second Edition)*.

As noted by the US Food and Drug Administration (FDA), such records are kept for the benefit of the company, for a specific purpose, and to support business processes and objectives: "The work that you do should be valuable to the organization, right? You're maintaining a record. You're maintaining the activities, not necessarily because you need to demonstrate it to the agency or to any other auditor. You're doing this work and maintaining this record because it becomes your source of truth for your organization down the road" [2].

Examples of GxP records supporting the medicinal product life cycle include those for clinical trials, master production and control, batch production, calibration, cleaning, deviation and corrective and preventative actions, and pharmacovigilance. GxP records also include formal validation plans and reports, including those for process validation and analytical method validation, and data that directly supports a GxP activity (e.g., process performance qualification batch data used in commercial products). Such validation plans, reports, and data should be managed using GxP document and records management approaches.

Computerized system validation plans and reports would be regarded as GxP documents in the same way. Other life cycle deliverables should be managed by applying normal and easily achievable good documentation practices, or, if in a format other than a traditional paper or electronic document, be maintained securely in an appropriately managed and controlled tool or system.

US FDA Narrow Scope

As noted by the US FDA, inappropriate application of Part 11 requirements can lead to unnecessary controls and costs and can discourage innovation and technological advances without providing added benefit to the public health: "...concerns have been raised that some interpretations of the part 11 requirements would (1) unnecessarily restrict the use of electronic technology in a manner that is inconsistent with FDA's stated intent in issuing the rule, (2) significantly increase the costs of compliance to an extent that was not contemplated at the time the rule was drafted, and (3) discourage innovation and technological advances without providing a significant public health benefit."

Part 11 also addresses narrow interpretation of scope: "We understand that there is some confusion about the scope of Part 11. Some have understood the scope of Part 11 to be very broad. We believe that some of those broad interpretations could lead to unnecessary controls and costs and could discourage innovation and technological advances without providing added benefit to the public health. As a result, we want to clarify that the agency intends to interpret the scope of Part 11 narrowly" [3].

According to narrow scope as described in the US FDA "Guidance for Industry. Part 11, Electronic Signature — Scope and Application," Part 11 applies only to records required by predicate rules. Computerized system life cycle records and IT process records are not required by predicate rules and are out of scope. These may be contrasted with records that are required by predicate rules, including batch, calibration, and laboratory product test records, and process validation and analytical validation data. The US FDA recommends that regulated companies determine, based on the predicate rules, whether specific records are Part 11 records and recommends documenting such decisions [3]. Establishing processes to achieve this (e.g., defined in an standard operating procedure) is suggested.

Computerized systems supporting the supply of medicinal products to multiple markets must also comply with GxP regulations applicable in those countries and not only US FDA record requirements. The GAMP approach to computerized systems compliance and record and data integrity is designed to satisfy a broad range of international requirements.

RISK-BASED APPROACH

Regulatory guidance from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the US FDA are clear that formality and extent of controls for any records and signatures should be based on risk. The focus should be on patient safety, not on compliance. The approach described in this article is aligned with such risk-based thinking.

MHRA

"Controls should be proportionate to the risk considering the type of document and the methods used for distribution and approval... Aspects to consider when assessing risk include ... whether there is a legislative requirement or GxP guidance for a signature. If there is, then the signature should be considered more critical and have proportionately greater control—for example when a QP [qualified person] certifies a batch of finished product to enable release for sale" [4].

The GAMP approach to computerized systems compliance and record and data integrity is designed to satisfy a broad range of international requirements.

FDA

"We suggest that your decision on how to maintain records be based on predicate rule requirements and that you base your decision on a justified and documented risk assessment and a determination of the value of the records over time" [3].

CRITICAL THINKING

Inappropriate application of rigid GxP record approaches and rules designed for other situations and contexts, without critical thinking, can discourage or prevent the use of best practice techniques and tools with no concomitant benefit to product quality or patient safety.

There have been cases of the use of standard tools being disallowed, being used in ineffective ways, or being inappropriately customized to meet spurious and unnecessary expectations. This can lead to unnecessary costs, lower quality product, decreased flexibility, and inferior process control. It can discourage innovation and technological advance, and it may prevent IT, software, and quality professionals from selecting and using the most appropriate and effective tools and systems to perform their duties.

For example, it is incorrect and unhelpful to argue that Part 11 requires a data audit trail to be applied to changes to software code, maintenance of system configuration records, or maintenance of user access privileges. A data audit trail is simply not an effective mechanism in those cases. It is also incorrect and unhelpful to insist on unnecessary Part 11 signatures, where there is no requirement for regulatory approval or legally binding equivalent of the individual's handwritten signature.

Other examples include printing maintained records in order to apply handwritten signatures, duplicating electronic records in a paper format, or duplicating other actions and activities in unnecessary and cumbersome paper processes.

System life cycle management and IT process management tools have been routinely used in other industries (including

automotive, consumer electronics, finance, energy, military, and aerospace) for decades, but they are often underutilized or misused in the pharmaceutical and other life science industries due to conservative interpretations of regulations, a misguided perception of regulatory inflexibility, and a lack of understanding of modern software and quality assurance practices. A modern approach to the use of such tools is described in Appendix D9 – Software Tools of *GAMP® 5 (Second Edition)* [1].

PRACTICAL IMPLICATIONS FOR QUALITY, COST, AND TIME TO MARKET

This is not just an academic or theoretical discussion: It has important practical implications. Inappropriate requirements, rules, and practices that do not enhance product quality and patient safety may act counter to current good practice. This can lead to activities that are unnecessarily costly, time-consuming, or ineffective. These may also be potentially harmful by adding complexity, duplication of information, and unnecessary customization.

The US FDA has described how an excessive focus on compliance may divert resources and management attention away from investments in quality and toward compliance activities like documentation, which do not directly lead to improved quality outcomes [5]. The US FDA has observed that a compliance-centric approach has not only hampered innovation in manufacturing and product development practices, it has also resulted in quality issues, and the perceived regulatory burden has contributed to outdated compliance practices [2].

This is, therefore, not purely a matter of interpretation of regulation but selecting and applying methods and techniques that best serve the interests of the patient and the public. From the perspective of the public, patient, shareholders, colleagues, and other company stakeholders, we must apply critical thinking to make pragmatic and logical decisions. For example, a practical question to ask when applying critical thinking is: "What approach provides the most value and gives the best outcome for the patient, the shareholders, and other company stakeholders in general?"

It is more beneficial to apply modern processes using state-of-the art tools and automation (designed specifically to support IT and software activity) that deliver systems that work instead of costly, inefficient, and unnecessary practices. These practices may have a negative impact on quality and may be based on a dogmatic reading or misunderstanding of regulations and historical perception.

Such judgements are not purely academic; there is a key ethical dimension. Decisions we make as an industry can impact time to market, limit the availability of medicines to patients, and drive up the price of medicines unnecessarily. We must apply ethical critical thinking and choose the option that gives the greatest benefit to the patient and the public.

BENEFITS OF USING APPROPRIATE AND EFFECTIVE TOOLS

The approach described in this article supports effective system life cycle processes, including version, change, and configuration management; requirements management and traceability; testing; verification; and defect prevention.

Practical examples of the advantage of using standard and widely used tools include effective configuration management and data management, automatic version control with auditing capabilities, change management and documentation, automated testing, and continuous integration and efficient issue tracking. Tools support and ensure both accountability and traceability in the coding, testing, and deployment processes.

Code modification, managed through a robust commit process, is recorded with details of the who, when, and how of the modification. Automated checks are performed at each commit. This allows for immediate notification to the developer in case of errors or defects, supporting the identification and addressing of issues during the life cycle. Regression tests are built in and are routinely run. The transparency and accountability that such tools automatically provide greatly contribute to the overall quality control process.

Key operational processes—including incident, problem, and configuration management; security; performance; capacity; and cybersecurity threat management—can only be performed effectively by using the appropriate tools. Traditional paper-based approaches cannot provide the desired controlled state.

As noted by the Cloud Security Alliance (CSA), a leading international organization dedicated to defining and raising awareness of best practices for a secure cloud computing environment, issues impacting good software development practices that hamper secure and effective deployment are manual and haphazard coding, testing, deployment, and patching practices:

"Without automated quality checks, manual coding can easily result in poor performing and insecure software that needs rework. In addition, manual and poorly-timed testing reduces the chance that vulnerabilities will be identified before deployment. Manual deployment and patching practices can result in insecure software from being released to production.

"Automated security practices are the core of process efficiency because they can reduce manual processes, increasing efficiency and reducing rework. Software quality can be bettered by improving the thoroughness, timeliness and frequency of testing/feedback. Processes that can be automated should be automated, and those that can't should be automated as much as possible or be considered for elimination" [6].

CONCLUSION

GAMP guidance makes a valuable distinction between GxP records supporting the medical product life cycle and required by a predicate rule, and non-GxP information, data, and artifacts that support computerized system life cycles and IT processes.

The unnecessary application of some customs and practices traditionally associated with GxP records, without critical thinking, to system life cycle and IT process records can lead to unnecessary costs and lower quality and process control. It can also discourage innovation, and may prevent IT, software, and quality professionals

from selecting and using the most appropriate and effective tools and methods to perform their duties.

Patient safety, product quality, and data integrity are best achieved by managing computerized system life cycle and IT process records through use of current good IT practice and software engineering principles supported by effective standard tools.

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REMOVING THE FRUSTRATION from Functional Risk Management

By Chris Reid, Sion Wyn, Charlie Wakeham, and Heather Watson

ISPE GAMP® 5: A Risk Based Approach to Compliant GxP Computerized Systems (Second Edition) [1], section 2.1.4 states "Quality Risk Management (QRM) is a systematic process for the identification, assessment, control, communication, mitigation, and review of risks."

ISPE GAMP® 5, Second Edition [1] states that, "Controls are developed to reduce risks to an acceptable level. Implemented controls are monitored during operation to ensure ongoing effectiveness."

Risks may be managed by elimination by design, reduction to an acceptable level, and verification to demonstrate that risks are managed to an acceptable level. Examples of risk control measures include designing failure detection mechanisms, implementing procedural monitoring, and testing to demonstrate that controls are fit for intended use.

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) harmonized guideline "Quality Risk Management Q9 (R1) [2]" defines two primary principles of QRM:

- "The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.
- The level of effort, formality, and documentation of the quality risk-management process should be commensurate with the level of risk."

We can derive from this that effective risk management is dependent on product and process understanding, critical thinking, and an understanding of how a computerized system supports the process.

PLANNING RISK ASSESSMENTS

QRM focuses effort where there is greatest risk to patient safety, product quality, and data integrity. However, experience shows that, too often, risk assessments are purely formal documentation exercises that have limited influence on the computerized system design or the implementation of controls to manage risk. There are a number of considerations when planning the risk assessment approach.

The value of risk assessment is limited by, for example:

- Failure to
  - include subject matter experts with product and process understanding who can clearly define the severity of a process or functional failure or who have the ability to detect a failure.
  - include subject matter experts with the appropriate system or technical understanding who can assess technical complexity and the probability of process or functional failure.
  - define appropriate mitigating actions to reduce risk.
- Risk assessments that are
  - conducted too early, so information is not mature enough to make valued judgement about risk.
  - conducted too late, so there is reluctance to modify design or conduct additional testing to reduce risk.
  - conducted against off-the-shelf functionality that implement industry best practice processes.
  - too granular (e.g., every single requirement is assessed rather than a feature area).

Scaling

High-level risk assessments conducted against processes or application modules can determine whether there is any patient safety, product quality, or data integrity risk. For example, this would include determining whether a finance module has any GxP risk. Processes and/or application modules that have no GxP impact are excluded from more granular functional risk assessments.

Lack of subject matter expertise

Even with the best-designed risk assessment process, a lack of subject matter expertise will lead to an erroneous outcome.

Process owners have process and product understanding and are best placed to determine the severity of risk scenarios. Functional experts have technical understanding of how the functionality is implemented and are therefore best placed to determine the probability of failure.

Generic risks

A number of risks can be anticipated in advance and managed as generic risks, particularly the failure modes. As such, it is not necessary to repeatedly evaluate generic risks. Table 1 provides some examples.

Granular or grouped requirements

Often, every single requirement is evaluated by the risk assessment. When requirements are written at a granular level, it is better to take a holistic approach and assess a related group of requirements, processes, or feature areas. In such cases, the primary risks requiring control can be identified rather than determining unnecessary controls for each specific requirement.

ISPE GAMP® Good Practice Guide: Enabling Innovation – Critical Thinking, Agile, IT Service Management [3] section 2.3.1 stresses the importance of logically grouping requirements in a structured manner. This approach significantly helps with the assessment of related requirements as a feature area or process area. (Note: it may be beneficial from a business perspective to conduct more granular risk assessments.)

Software/configuration error

Risk assessments often record "software/configuration error" as a risk scenario. This is the cause of the failure and is a superfluous and obvious statement. The failure scenario should clearly state how patient safety, product quality, or data integrity could be impacted.

Off-the-shelf solutions

Off-the-shelf solutions are designed by vendors to reflect industry best practice. Solution evaluation should confirm that this is the case. The likelihood of failure is low for mature off-the-shelf solutions. Therefore, for such solutions, the primary focus should be to determine functional severity to define the scope of validation effort. Assessment of probability of failure and detection mechanisms will be of limited value.

Novel solutions

Novel solutions are typically new or innovative solutions that may include limited process or functional understanding. It is essential that sufficient understanding is established before the risk assessment is started. As discussed previously, a risk assessment may evolve iteratively with the solution design. Process owners may require training to better understand the solution prior to commencing risk assessments.

INTEGRATING RISK ASSESSMENTS INTO THE DESIGN PHASE

Risks may be initially evaluated against business processes and/or requirements. However, for complex systems, risks should be further evaluated during the design and configuration phase. Additional information provided by design and configuration records is useful in confirming risk assessments or in revising to address additional information relating to detectability or the likelihood of failure.

Table 1: Examples of anticipated risks.

Feature	Generic Failure Scenarios
Data Interface	Data transfer does not trigger when required Data transfer does not recover following interface failure Data is incomplete Data is not loaded/mapped correctly
Reports	Report layout is incorrect Data is incomplete/incorrect Data resolution is incorrect/inaccurate Report is not generated when required Report is not saved Report is not approved
Data	Data entered by unauthorized person Data entered out of range Data not saved Data not stored accurately or in wrong data item Data approved by unauthorized person Data accessible by unauthorized person Data not protected against loss

Inform Design

Risk assessments are often conducted as a separate activity from process and functional design. As such, risk assessments are used to assess rather than to inform the design. Risk assessment should be an integral part of the design, where the risk assessment evolves with the design to establish a robust solution, rather than being handled by a separate team that conducts the risk assessment to challenge a completed design.

Agile frameworks cater to this very well when the risk assessment is an integral part of user story development, and when it is built into sprint planning, sprint review, and sprint retrospective—when the current risk conclusions and selected controls are developed and continuously monitored.

Evaluate Controls

Often the focus of risk assessment is to formulate test plans and test scenarios. The primary focus of risk assessment should be to ensure the designed controls are adequate. Testing is then used as one approach to verify that designed controls function correctly.

Consider Different Designs

For complex solutions, a different design or configuration may be used to deliver the same requirement. For example, this would

Table 2: Components of a risk assessment.

Risk Assessment Component	Description	Considerations	
Severity	The potential impact on patient safety, product quality, or data integrity. • Direct impact: High • Indirect impact: Medium • Negligible or no impact: Low	When to evaluate?	When the process and/or user requirements are defined and understood
		Who should evaluate?	Process owners
		What does it tell us?	The potential harm
		When is it relevant?	Always
		What do we do about it?	• Scale the validation effort; higher severity leads to greater validation effort • Identify and/or design controls specifically to control the harm and to minimize the impact on safety and/or quality to an acceptable level
Probability/Likelihood of Failure	Software is more likely to fail if it is a new code or complex configuration. Out-of-the-box software is well proven and less likely to fail. • Non-configured off-the-shelf software: Low • Configured software: Medium • Customized software: High Note: These are guidelines only. Complex configuration could increase the probability, and low-complex custom software could be medium. Probability should also consider human factors/error.	When to evaluate?	During design and configuration
		Who should evaluate?	Functional subject matter experts (SMEs)
		What does it tell us?	Likelihood that the function will fail
		When is it relevant?	For solutions that have complex design and configuration
		What do we do about it?	• Lower the probability by verifying that the function works • Avoid customized solutions when possible • Design should consider human factors/error and minimize the probability of such errors (e.g., with data entry verification)
Detectability	Should the system malfunction, will it be readily detected? • Automated or procedural detection that specifically looks for the failure: High • Thorough observation and/or focused data review, including consideration of audit trails: Medium • Unlikely: Low	When to evaluate?	When process design is complete
		Who should evaluate?	• Process owners who understand how failures could be detected • Functional SMEs who understand how the detection functionality works
		What does it tell us?	• Whether there is a failsafe mechanism to limit the risk of patient safety, product quality, or data integrity • The detection mechanism should be verified
		When is it relevant?	Most valuable for high-severity functionality
		What do we do about it?	• Consider alternative detection mechanisms if the risk is high • Verify that the detection mechanism is in place and working

occur when deploying multiple releases to different organizational units for a corporate solution (e.g., enterprise resource planning). In such cases, it is possible that the severity, probability of failure, and detectability could change.

For example, if the same requirement applies to similar processes but different products of differing risks, the severity of failure may differ. If the complexity of the design and configuration is different, the likelihood and detectability of failure may be different. As such, risks need to be reassessed considering different product severity, design, and configuration.

DETERMINING PROBABILITY OF FAILURE

GAMP Guidance

ISPE GAMP® 5 (Second Edition) [1] software categories provide high-level guidance on the probability of functional failure and should not be taken literally. Category 5, Customized Software, suggests a high probability of failure. However, if the code comprises only 20 lines, then the probability is likely to be less. Similarly, configuration, especially on large corporate applications such as enterprise resource planning systems, may be complex and need to be considered as a high risk of failure. Input from functional experts is essential when considering the likelihood of failure.

CONDUCTING RISK ASSESSMENTS

Timing

Risk assessments are often conducted too early or too late, or they take too long to complete due to protracted discussions. Conducting risk assessments early without sufficient process and/or product understanding can lead to insufficient information to make valued judgements about potential failure scenarios and severity of failures. Further, assessing the likelihood of failure before solution design and configuration phases may mean there is insufficient knowledge to correctly evaluate the likelihood of failure.

Completing risk assessments late limits the influence of the risk assessment outcome on the solution design and testing. Risk assessments completed after design approval are unlikely to lead to design changes to lower the risk and are too late to input to test planning.

Testing

Risk assessments use testing against designed controls as a means of reducing risk. Testing confirms that designed controls are fit for intended use and reduce the probability of functional failure. However, risk assessments often simply state "to be tested in functional and acceptance testing," rather than stating the specific test objectives arising from the risk scenario. As such, test teams must rethink the outcome of the risk assessment to determine what needs to be tested.

Planning Considerations

There is no doubt that risk assessment in the context of wider risk management is essential to ensuring computerized systems that are fit for intended use. However, mechanical application of risk assessments without critical thinking can lead to a poor outcome that has little influence on the design and validation of a solution. Table 2 explains the different components of a risk assessment and other considerations, such as when and by whom the evaluation will be done.

MANAGING RISK ASSESSMENTS

Risk assessment is only an element of the risk management process. Controls must be verified and risks must be monitored to ensure the risk treatment is effective. As such, the risk assessment must be managed in a way that can be readily maintained as experience during the project and operational phase is gained. Thus, risk assessments might be managed within a tool or as an integral part of the solution design.

CONCLUSION

Risk assessment is essential if risks are to be effectively managed during the project and/or operational phase. However, the output of the risk assessment is of limited value if it is not conducted by a team with the necessary process, product, and functional understanding. Conducting risk assessments prematurely may lead to invalid assessment of the overall risk. Conducting risk assessments too late will limit the opportunity to address design flaws and effectively test processes and functionality.

Mature out-of-the-box functionality is unlikely to present a significant risk, and therefore risk assessment should focus on identifying functionality that impacts patient safety, product quality, and data integrity to scope the validation effort. Complex systems that require significant design and/or configuration should be assessed for the likelihood of failure and the ability to detect failures that might arise from the incorrect design or configuration.

An efficient risk assessment process conducted at an appropriate level by the right SMEs will significantly increase the likelihood of delivering a solution that is fit for intended use. Risk assessment is a means of evaluating the effectiveness of designed controls and, where necessary, taking action to lower the risk through designing, testing, or proceduralizing activities to lower the risk. Risk management is primarily a process for identification and control of quality risks. As stated by the US FDA, "our primary focus …[is] to minimize the risks to the public health" [4].

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CELEBRATING 25 YEARS of GAMP® Americas

By Brandi Stockton, Lorrie Vuolo-Schuessler, and Charlie Wakeham

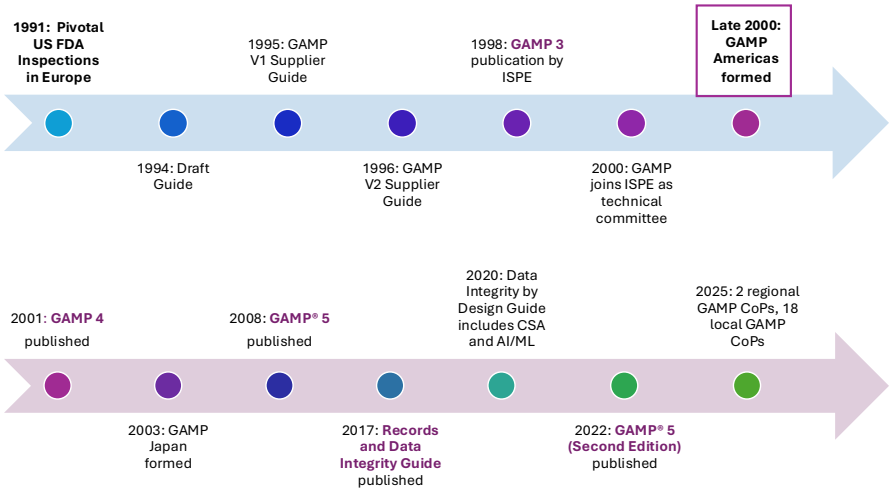
This special anniversary article addresses the history and milestones that define the GAMP Community of Practice (CoP). In celebration of the 25th anniversary of the creation of GAMP Americas, we reflect on the vital role GAMP Americas has played in that journey. We commemorate key accomplishments of its members, share recent activities, and look ahead to the future of GAMP Americas.

ORIGINS OF GAMP AND ITS GUIDES

The GAMP CoP originated in the United Kingdom in 1991. Led by a team of leading innovators from within the pharmaceutical engineering sector, the forum steering group included David Selby, PhD, then with Glaxo International Quality Assurance; Clive Taylor, then of Wellcome plc; Tony Margetts, PhD, then of Zeneca Pharmaceuticals; and, Annis Bratt, then with SmithKline Beecham. The group was formed in response to US Food and Drug Administration (FDA) inspections that increased focus on the management and controls of automated systems. Under the group's leadership, industry experts worked to create draft guidance to improve the understanding and communication of regulatory expectations for the use of automated systems supporting Good "x" Practice (GxP) activities. The history of GAMP can be traced through some of the guidance documents created and key milestones shown in Figure 1.

The *Supplier Guide*, or *GAMP Version 1.0* as known today, was published in electronic format in March 1995 [1]. It addressed expectations from the US FDA and the European Commission's Good Manufacturing Practice recommendations from Annex 11.

Figure 1: Key GAMP milestones and publications.



The second edition of GAMP followed in May 1996 with new content in response to comments from the European Commission and the US FDA [2]. In March 1998, GAMP Version 3.0 [3] was published with funding from ISPE. It included user and supplier guides. Its publication was a foretaste of GAMP becoming a technical subcommittee of ISPE in 2000.

Previously, only pharmaceutical companies were directly involved in writing GAMP guidance. The Supplier Forum was established in 1995 with support from the Medicines and Healthcare Products Regulatory Agency (MHRA). Guy Wingate, PhD (retired, VP & Compliance Officer, GlaxoSmithKline), served as chair of the forum with the goal of providing a community for UK and European vendors, suppliers and consultants, and regulators to discuss the practical application of GAMP guidance. This group was fully incorporated into GAMP in 2000, from which point pharmaceutical companies and vendors would work directly together to write and develop future GAMP guidance.

The *ISPE GAMP® 4 Guide for Validation of Automated Systems* was released in December 2001 and represented a major revision and new content addressing regulatory and technological developments [4]. Key members of the newly formed GAMP Americas—Paul D'Eramo, Arthur (Randy) Perez, PhD, and Rory Budihandojo—contributed significantly to this updated guide created through a truly international effort, with representatives from sponsor companies, suppliers, and regulators globally. This version of the industry-leading guide broadened the scope to include a wider range of regulated healthcare industries, whereas previous iterations had only focused on systems used for GMP systems. *GAMP 4* applied to all regulated systems and included greater focus on user responsibilities and details on the operational phase.

NO LONGER AN ACRONYM

Prior to the release of *GAMP® 4*, GAMP had originally been an acronym for Good Automated Manufacturing Practice. With the scope broadened in *GAMP® 4* to include much more than just automated manufacturing, GAMP instead became a name, trademarked by ISPE, and the acronym was discontinued. GAMP now represents guidance applicable to computerized systems used in regulated activities covered by Good Laboratory Practice, Good Clinical Practice, Good Distribution Practice, Good Pharmacovigilance Practice, Medical Device Regulations, and GMP. Collectively, these are referred to as GxP.

TAKING TECHNOLOGY FROM THEORY TO PRACTICE

ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems was released in 2008, with the GxP in its title reinforcing the broader scope [5]. As with all GAMP guidance, this version was created in response to changes in the industry and in regulatory expectations. In particular, the US FDA's promotion of risk-based approaches and the publication of ICH Guideline Q9 on Quality Risk Management in 2006 [6]. *GAMP® 5* emphasized product and process understanding and offered a practical application of risk-based approaches to computerized systems

Figure 2: GAMP wins committee of the year for a second time.

Technology and methodology continued to evolve after the publication of *GAMP® 5*, and GAMP guidance documents have led the way in facilitating industry adoption of innovative solutions and new technologies within the often conservative life sciences industry. For example, GAMP published guidance on using and managing cloud computing and agile methodologies as far back as the 2012 *ISPE GAMP® Good Practice Guide: A Risk-Based Approach to Testing GxP Systems* (*Second Edition*).

Computer software assurance (CSA) approaches were written into the 2020 *ISPE GAMP® Records and Data Integrity Good Practice Guide: Data Integrity by Design* [7] which was published two years before the US FDA released it's draft guidance "Computer Software Assurance for Production and Quality System Software" in 2022, by which time, the full application of computer software assurance (CSA) principles had already been adopted and expanded in the second edition of *GAMP® 5*. The Guide also includes guidance on blockchain and artificial intelligence/machine learning (AI/ML), providing companies with a framework to leverage these advances into their regulated applications.

The suite of 15 current GAMP® good practice guides has recently been enhanced with an update to the guide on eClinical data. Later this year, ISPE will publish the first-of-its-kind Good Practice Guide on AI/ML technology. It was led and produced by Brandi Stockton, Founder and Managing Partner with the Triality Group, LLC, and Chair of ISPE GAMP Americas CoP Steering Committee.

Recognizing its impact within the life sciences industry, the GAMP Global Steering Committee won ISPE's Committee of the Year in 2016 and again in 2022 (see Figure 2).

Having originated in Europe, GAMP Americas was established in 2000 as the first GAMP committee outside of Europe, providing a positive step toward global recognition and participation in the GAMP community. The GAMP Americas CoP Steering Committee introduced GAMP principles and methodologies into the US via a forum event, which included keynotes by Selby, Wingate, and D'Eramo.

During the initial GAMP Americas Forum, several special interest groups (SIGs) were formed to begin working on various GAMP good practice guides (e.g., the GAMP Forum Laboratory Systems SIG, and the Global Information Systems SIG). Although these teams started and were led by members of GAMP in the US, and overseen by the GAMP Americas CoP Steering Committee,

Figure 3: GAMP around the world.

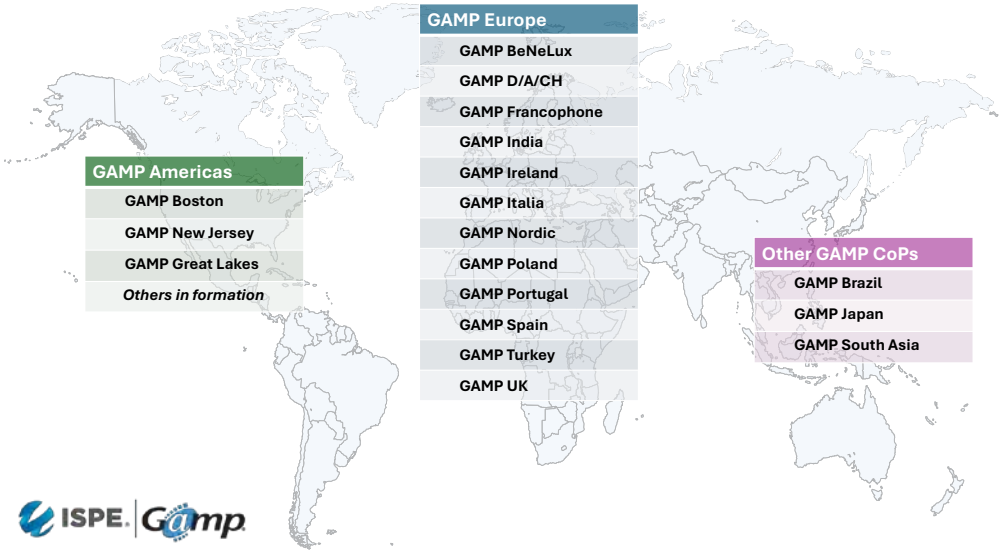


Figure 4: GAMP Americas founding members and Chairs over the last 25 years.

GAMP Americas Trailblazers and Leaders

Thanking our Founding Members

- Rory Budihandojo (Chair)
- Barbara Nollau
- Ed Kanczewski
- Jim John
- Kevin Martin
- Mike Wyrick
- Paul D'Eramo
- Randy Perez

Celebrating 25 years of GAMP Americas Chairs

- 2000 – 2001 Rory Budihandojo
- 2002 – 2008 Randy Perez
- 2007 – 2008 Rory Budihandojo
- 2008 – 2009 Paige Kaine
- 2010 – 2012 Kevin Martin
- 2013 – 2015 Mike Rutherford
- 2016 – 2019 Eric Staib
- 2020 – 2023 Lorrie Vuolo-Schuessler
- 2024 – Present Brandi Stockton

they were open to and supported by GAMP members throughout the entire international GAMP community.

GAMP continued to grow globally through the combined efforts and dedication of GAMP Americas and the original GAMP founders and leaders in Europe, later formalized into GAMP Europe, which today has 12 local CoPs. The 2003 creation of GAMP Japan saw GAMP expand into Asia Pacific for the first time; 20 years later, GAMP South Asia was formed in the region to promote and support GAMP across Australia, Indonesia, Malaysia, New Zealand, Philippines, Singapore, and Thailand. An overview of the GAMP communities around the world is shown in Figure 3.

The GAMP Americas Steering Committee has always maintained a seat for representation from the US FDA. Robert D. Tollefsen, of the US FDA's Office of Regulatory Affairs (ORA), was an active and valued member of the Americas Steering Committee for many years, providing his insight into discussions and expert review of many GAMP guides. GAMP Americas is now privileged to count Seneca Toms, MS, RAC, of the US FDA's Center for Drug Evaluation and Research as among its current members.

The formation of GAMP Americas and the boundless dedication of its founding and ongoing members have strengthened and expanded the GAMP community through its quarter century of operation, and Figure 4 shows the original committee and the committee chairs through its history.

GAMP AMERICAS ACTIVITIES

GAMP Americas has been a very active regional GAMP CoP. Its steering committee has led and/or collaborated with the creation of many GAMP good practice guides. Members of GAMP Americas have also actively participated with other areas of the GAMP community in presentations and workshops during ISPE meetings and conferences.

In their first decades, the GAMP Americas Steering Committee held multiple forums and meetings primarily in the northeast

Figure 5: Some of GAMP Americas inspirational members.

Mike Rutherford
- 2013 – 2015 GAMP Americas Chair
- 2015 Max Seales Yonkers Member of the Year
- 2015 – 2017 GAMP Global Chair
- 2016 Joseph X. Phillips Award
- 2017 – 2024 ISPE Board of Directors
- 2022 – 2023 Chair, ISPE Board of Directors
- Multiple guide author

Arthur (Randy) Perez
- 2002 – 2006 Americas Chair
- 2005 Max Seales Yonker Member of the Year
- 2005 – 2013 ISPE Board of Directors
- 2011 – 2012 Chair, ISPE Board of Directors
- 2014 Richard B. Purdy Award
- Multiple guide author
- ISPE GAMP trainer

Winnie Cappucci
- 2010 – 2013 GAMP Global Chair
- 2013 Richard B. Purdy Award
- Multiple guide author
- ISPE GAMP trainer

Lorrie Vuolo-Schuessler
- 2020 – 2023 GAMP Americas Chair
- 2023 Richard B. Purdy Award
- Multiple guide author
- ISPE GAMP trainer

Brandi Stockton
- 2022 Winning Team Coach, ISPE EL Hackathon
- 2023 – Present GAMP Americas Chair
- Multiple guide author
- ISPE GAMP trainer

United States. They also held full day forums at ISPE conferences in the United States.

During the last several years, the GAMP Americas Steering Committee has been working to offer more opportunities to GAMP members throughout the Americas by starting local ISPE Chapter GAMP CoPs. These new GAMP CoPs provide local GAMP chapter members with ongoing access to GAMP experts, networking opportunities, and platforms to showcase work and accomplishments, share experience, and cultivate professional growth and visibility within the industry. To date, several new GAMP CoPs have been chartered under GAMP Americas including the ISPE Boston Chapter GAMP CoP, the New Jersey Chapter GAMP CoP, and the Great Lakes Chapter GAMP CoP.

AWARDS AND ACHIEVEMENTS

Members of GAMP Americas have also been awarded multiple ISPE international honor awards, including the Max Seales Yonker Award that honors an ISPE member who has made the most significant contribution to the society during the last year, the Richard B. Purdy Distinguished Achievement Award given to an ISPE member who has made significant, long-term contributions to the society, and the rarely given Joseph X. Phillips award that recognizes the extraordinary contributions of its recipients. Among them, GAMP Americas members have been awarded eight ISPE individual honor awards. Figure 5 highlights the achievements of some of the most inspirational members of GAMP Americas.

Cappucci said: "I loved every minute I worked with the GAMPers and still do. What a changing of the guard and a firm foundation for the future."

Selby reflected recently on GAMP's continual growth and success from its beginnings in 1991: "It is really impressive to see how the baton has been passed on and enthusiastically taken up by each new generation. Hearty congratulations to all who had the faith to work together in those early days and have continued after me for making GAMP what it is today and so much better than I could ever have imagined."

SUCCESSION AND NEW MEMBERS

Membership on a GAMP Steering Committee, Americas or other, has always been based on merit (i.e., demonstrated leadership and/or involvement with GAMP activities through extensive volunteering). Some of our committee members have been investing their own time and expertise into GAMP over decades and their input has been foundational to its success.

New members and new ideas, especially from our industry's Emerging Leaders, are not only desirable but essential to keep GAMP energized and topical. GAMP Americas has been inspirational in recruiting new steering committee members and engaging with universities, students, and Emerging Leaders, collectively strengthening GAMP's future.

To encourage succession planning and create opportunities for recruiting new steering committee members, a recent revision to guiding principles applicable to all GAMP CoPs has introduced a limit on the duration of membership on its committees.

Randy Perez and Mike Rutherford: Thank you for your exceptional contribution!

Two of GAMP's most respected leaders, Randy Perez and Mike Rutherford, are now exiting the Americas Steering Committee under the revised principles. Their volunteer highlights and achievements are vast (see Figure 5) deserving of much more than a few bullet points.

A former senior leader within Novartis and a founding member of GAMP Americas, Perez has continued to devote much of his time to the furtherment of GAMP since his retirement in 2015. During recent years, he has been an active GAMP trainer, acted as an important liaison between GAMP and other ISPE initiatives, and is always willing to share his ideas for GAMP direction and strategy.

Any ISPE Affiliates or Chapters interested in including GAMP topics at a meeting, please contact GAMP Global or GAMP Americas Leadership. It is vital that all ISPE activities have consistent, aligned messaging around GAMP topics.

Rutherford had an extensive and distinguished career with Eli Lilly and then Syneos Health before retiring in 2023. During his successful executive roles, and continuing after his retirement, he has always made time for GAMP and ISPE. He was instrumental in driving and developing data integrity best practices, many of which are captured in the *ISPE GAMP® Records and Data Integrity Guide*, which he co-led with Sion Wyn (Conformity Ltd.) and Nigel Price (QCDI Ltd.). No distance was too far, with him sharing his knowledge at ISPE conferences as far as South Korea and Singapore.

Although Rutherford is leaving the steering committee, we know he will continue to be one of GAMP's strongest supporters. In recognition of the universally high esteem in which he is held within ISPE and GAMP, in September, he was named Interim President and CEO of ISPE and the ISPE Foundation, a post he held until December. Thank you to both for exceptional contributions over the years.

In addition to Perez and Rutherford, there have been many extraordinary GAMP Americas Steering Committee members who have made significant contributions to GAMP Americas throughout the years. Although there are too many to list here, we thank them all for their contributions.

The same succession planning has also happened within the GAMP Global Steering Committee. In addition to Perez and Rutherford, we are also saying goodbye with a heartfelt thanks to Guy Wingate, PhD, (Chair GAMP Council 2000–2010 and ISPE Board of Directors), Chris Reid (Chair GAMP Global Steering Committee 2017–2019 and ISPE Board of Directors), and Chris Clark (Chair GAMP Editorial Review Board 2009–2023). They have all been giants of GAMP and will be missed.

We've sadly lost Anthony (Tony) Trill who passed away in August. He was a long-time ISPE member with a decades-long career in the pharmaceutical industry with expertise in Good Manufacturing Practices (GMP) standards. Tony was a major influencer and contributor in the early days of GAMP guidance and deserves much credit for getting European regulators involved with and supporting GAMP.

A BRIGHT FUTURE FOR GAMP AMERICAS

The knowledge-sharing forums adopted by GAMP Americas and its new local GAMP Community of Practice (CoP) are drawing in attendees both within and outside of current ISPE and GAMP membership. They are attracting new event sponsors and tempting inactive sponsors back after a hiatus of several years. There is new and renewed interest from regulated companies (including supporting chapter/leading committees), increased interest from emerging leaders/students, and increasingly inspiring other ISPE Chapters within the Americas to establish their own local CoPs. The GAMP Boston event achieved a massive level of engagement from younger professionals with approximately 20% of the attendees currently attending school full time.

The GAMP Forums bring much more than just a seminar approach as evidenced by this feedback from one of our members attending our Great Lakes Forum event:

"For me, the ISPE Great Lakes Chapter GAMP Forum in Chicago wasn't just an educational event, it was a vibrant hub of industry expertise and camaraderie. I met so many fantastic people from the industry, each bringing their unique experiences and insights. This gathering was truly an exceptional experience, blending learning with meaningful connections. The sessions, ranging from critical thinking to the latest in Machine Learning and AI, were not only informative but also inspiring. It's rare to find an event where you can so deeply immerse yourself in the spirit of innovation and collaborative problem-solving," said Jahnavi Vellanki, a laboratory systems validation specialist with Labcorp and Great Lakes Forum attendee.

With GAMP events in 2023 in Princeton and Raleigh, and forums in 2024 in Chicago, Indianapolis, and Boston, GAMP's accessibility throughout the Americas is growing, making it easier than ever to get engaged. There are now links from GAMP Americas to GAMP Brazil, ISPE Mexico, and ISPE Canada Affiliates. The energy in the current GAMP Americas Steering Committee is spreading through its geography.

Any ISPE Affiliate or Chapter in the Americas interested in establishing a GAMP CoP, please contact GAMP Americas leadership.

GETTING INVOLVED

GAMP experts around the world are here to help you plan events around digital transformation and to connect you with exactly the right people to help you get involved as a GAMP volunteer.

GAMP topics may overlap with and complement other CoPs. We have experts from our SIGs that can present on many topics with case studies including, but not limited to, software automation and artificial intelligence, blockchain and distributed ledger, data (integrity, quality governance, management), infrastructure, cloud, Agile software development, CSA, and more.

For anyone interested in becoming involved with GAMP:

- Ensure you have selected your affiliate or chapter in your ISPE profile
- Contact your local affiliate or chapter (details can be found on the ISPE affiliates and chapters page)
- Select GAMP CoP in your ISPE profile
- Post into the GAMP community in ISPE Engage—we will respond
- Volunteer for a GAMP SIG or other specific activities: Reach out to any GAMP leader in your region through either the ISPE membership directory or LinkedIn messaging. We are here to help and glad to connect to new enthusiasts

Any ISPE Affiliates or Chapters interested in including GAMP topics at a meeting, please contact GAMP Global or GAMP Americas Leadership (depending on your location). It is vital that all ISPE activities have consistent, aligned messaging around GAMP topics. We are happy to help you do this by recommending speakers, reviewing materials, and promoting your event through our networks, committees, and communities.

- GAMP Americas chair: Brandi Stockton, bstockton23@outlook.com
- GAMP Americas past chair: Lorrie Vuolo-Schuessler, lvschuessler@verizon.net
- GAMP Global chair: Charlie Wakeham, charlie.wakeham@wakeuptoquality.com

MORE ON GAMP

A more detailed discussion of GAMP's beginnings and the community's current objectives was published in "Happy 30th Anniversary to the GAMP Community of Practice!" in the May/June 2021 issue of *Pharmaceutical Engineering* [9] written by Siôn Wyn, who has provided exceptional expertise and dedication to the GAMP community for well over 20 years and continues to do so, bringing significant benefit to our industry.

EDITOR'S NOTE: In more recent years, David Selby, worked for Glaxo Wellcome Operations, Barnard Castle, and later Voss, until retiring in 2017. Tony Margetts currently serves as the principal consultant for Factorytalk in Bangkok.

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About the authors

Brandi Stockton is founder and managing partner of The Triality Group, LLC, which provides technology, quality, regulatory, and compliance consulting services for the life sciences industry. She has over 20 years of GxP experience, with a specialization in computer systems quality and data integrity. She is vice president of the ISPE Great Lakes Board of Directors, a member of GAMP Global, chair of GAMP Americas, co-lead of the GAMP Global Software Automation and AI SIG, and an active member of the ISPE AI® CoP. Brandi joined ISPE in 2014.

Lorrie Vuolo-Schuessler retired from her industry role as senior director computer systems quality and data integrity at Syneos Health in 2022 and continues to actively contribute to GAMP through SIGs and steering committees and delivers GAMP training courses on behalf of ISPE. She received the ISPE Richard B. Purdy Distinguished Achievement Award in 2023 in recognition of her 20-plus years of contribution to ISPE and GAMP, including most recently serving as chair of the GAMP Americas Steering Committee. She has co-authored multiple GAMP guides and articles. She joined ISPE in 2002.

Charlie Wakeham offers consultancy services and training in computerized systems quality and data integrity through her company WakeUp to Quality. She is the current chair of the GAMP Global Steering Committee, leading more than 5,000 members of the GAMP CoP, as well as serving on numerous other GAMP and ISPE committees. Her career over 25 years has focused on GxP computerized systems and quality. Charlie received the ISPE Max Seales Yonker Member of the Year Award in 2019 for her GAMP volunteer work and training of regulatory agencies. She joined ISPE in 1999.

ISPE Announces the 2024–2025 International Board of Directors and Honor Award Winners

By Marcy Sanford

The new ISPE International Board of Directors was introduced, the gavel was passed to a new Chair, and Honor Award Winners were announced on 15 October 2024 during the 2024 ISPE Membership Meeting and Awards Lunch in Orlando, US, during the 2024 ISPE Annual Meeting & Expo.

ISPE Board of Directors Immediate Past Chair Scott W. Billman (right) passes the gavel to incoming Chair Jeffrey A. Biskup, PE, (left).

CHANGES TO THE BOARD

Incoming Chair Jeffrey A. Biskup, PE, Executive Chairman of the Board at CRB, began his year as Chair. Outgoing Chair Scott W. Billman, Senior Vice President, Global Engineering, Technology, and Facilities, Solventum, moved into the Past Chair position of the International Board's officers. The Membership Meeting included presentations by Billman, Biskup, and Michael Rutherford, 2024 Interim ISPE President and CEO, as well as reports on the financial health of ISPE and an update on the ISPE Foundation.

Billman gave an overview of ISPE's accomplishments in 2024, which included the following:

- Distributing $154,785 to Affiliates and Chapters for local membership projects
- Reaching 22,000 members
- Starting new Communities of Practice (CoPs) for Sustainability and artificial intelligence (AI)
- Expanding professional development and custom training offerings
- Continuing engagement with regulatory agencies

"ISPE is positioned to drive expanded knowledge sharing across the industry," Billman told attendees. He also thanked outgoing board members for their contributions as they stepped down from the board. Past members include:

- Nina S. Cauchon, PhD — Director, Regulatory Affairs–CMC, Amgen Inc.
- Teresa Minero — Founder and CEO, LifeBee, a Product-LifeGroup Company
- Monique L. Sprueill, PMP — Director and GCP Process Quality Lead, Bristol Myers Squibb
- Hirofumi Suzuki, PhD — Manager, Regulatory Affairs CH Japan, Bayer Yakuhin Ltd.
- Michael L. Rutherford — Interim President and CEO, ISPE and ISPE Foundation. Resigned from the board in 2024.

HIGHLIGHTS AND UPDATES

Rutherford welcomed attendees to the Membership Meeting and spoke about the ways the 22,000 ISPE members in 120 countries are helping shape the future of the pharmaceutical industry. "Our subject matter expertise is growing with CoPs. Guidance documents have added new ways to subscribe through institutional and corporate licenses. Conferences continue to highlight the innovative advancements within the industry through key education sessions, and the ISPE Foundation continues to provide professional development grants to students and recent graduates."

James A. Breen, Jr., ISPE Foundation Board of Directors Vice Chair, 2022–2024, Vice President, Global Engineering and Technology, Johnson & Johnson Innovative Medicines, introduced the ISPE Foundation Board and gave an overview of the ISPE Foundation's accomplishments for 2024, including the Technology without Borders Program, which will provide essential ISPE guidance documents and delivered nearly $250,000 worth of training in Portuguese to individuals in Brazil, and the Workforce Diversity Pillar, which awarded a scholarship through the Women in Pharma® program.

He also thanked the ISPE Delaware Valley Chapter for establishing the Delaware Valley Chapter Scholarship Fund. The largest Affiliate/Chapter gift in the Foundation's history, the Fund provides academic scholarships to aspiring students in the Mid-Atlantic region. This enables them to concentrate on their education and career development in the pharmaceutical industry.

THE 2024–2025 INTERNATIONAL BOARD OF DIRECTORS

Pictured from left are David Churchward, Jeffrey A. Biskup, PE, Mike Martin, Vivianne Arencibia, Vivien Santillan, Sarah Pope Miksinski, PhD, Shanshan Liu, Liz Dooley, MSc, Rebecca Roscher, Michael Rutherford (2024 ISPE Interim President and CEO), Timothy J.N. Watson, PhD, and Scott W. Billman
Not pictured: Ylva Ek, Norman Goldschmidt, James Grunwald, and George Singewald, PhD.

Officers

Chair
Jeffrey A. Biskup, PE
Executive Chairman of the Board, CRB

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

Treasurer
Ylva Ek
Founder, Robur Life Science Advisory AB

Secretary
Vacant at Time of Printing

Past Chair

Scott W. Billman
Senior Vice President, Global Engineering, Technology, and Facilities, Solventum

Ex Officio Non-Voting Member

Mike Martin
President and CEO, ISPE, ISPE Foundation

Directors

David Churchward
Head of Operations Quality, Compliance and External Affairs, AstraZeneca

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

Norman A. Goldschmidt
President, Genesis AEC

James Grunwald
Senior Vice President US Business Development, Arcadis

Shanshan Liu
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Vivien Santillan
Regional Director, Asia, Novatek International

Georg Singewald, PhD
SVP, Global Head of Quality & Compliance, Roche Pharma & Genentech

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

Ex Officio

Emerging Leaders Representative (non-voting)
Rebecca Roscher
Project Manager, Bayer AG

2024 INTERNATIONAL HONOR AWARDS

The 2024 ISPE Honor Awards were distributed to recipients by Michael L. Rutherford, Jeffrey A. Biskup, PE, and Scott W. Billman.

2023 ISPE Roger F. Sherwood Article of the Year Award

Winners were awarded for *Pharmaceutical Engineering*® content published during 2023.

"Comparability Considerations for Cellular and Gene Therapy Products," published in the November/December 2023 issue by Andrew Chang, PhD, Katherine Donigan, PhD, Kathleen Francissen, PhD, Sam Gunter, MPP (pictured), and Emily Hernandez, PhD

2024 ISPE International Emerging Leader Hackathon Winning Team

Milton Engineering

Team members

- Bonnie Brown
- Denzel Dollano
- Marcella Ayala
- Susan Gamboa
- Tiffany Lee

2024 Company of the Year Award

Takeda

2024 ISPE Affiliate and Chapter Excellence Award

Chesapeake Bay Area Chapter

2024 ISPE Committee of the Year

Pharma 4.0™ Baseline Guide Team

2024 ISPE Max Seales Yonker Member of the Year Award

Niranjan S. Kulkarni, PhD — Senior Director, Consulting Services, CRB

2024 ISPE Richard B. Purdy Distinguished Achievement Award

Roger Nosal — Head of Global Regulatory Strategy and Submissions, NGT Biopharma

2024 ISPE Joseph X. Phillips Professional Achievement Award

Antonio (Tony) R. Moreira, PhD — Vice Provost, Academic Affairs, University of Maryland; 2020–2024 Chair, ISPE Foundation.

The award was granted posthumously. Members of the Moreira family, pictured above, accepted the award on behalf of Tony.

VOLUNTEER PROFILE

MARK CHERRY, GAMP® EUROPE COMMUNITY OF PRACTICE CHAIR

Mark Cherry is the IT Compliance Director and GXP subject matter expert at AstraZeneca. A chartered engineer, he has been with AstraZeneca for 22 years and was previously with GlaxoSmithKline in a variety of computer compliance and engineering roles. He has been a member of ISPE since 1999.

In addition to serving on the GAMP Europe Community of Practice (CoP) as Chair, he led the team that produced the second edition of the *ISPE GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems*. He was a core team member in the development of the second edition of *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* and the *ISPE GAMP® Good Practice Guide: Enabling Innovation – Critical Thinking, Agile, IT Service Management*. In 2017, he played a key role in forming GAMP CoP in India.

What do you do in your current role?

I provide IT risk consulting and partnership for AstraZeneca IT areas that support the business units in order to ensure existing and emerging technology-related risks are identified and appropriately mitigated or escalated. I also have the role of GxP "subject matter expert" for AstraZeneca IT, ensuring that we have appropriate IT standards to meet pharmaceutical regulatory requirements. The aspect of being able to work with departments across the entire enterprise—research and development, manufacturing, etc.—is something I really enjoy.

I started my career in engineering within manufacturing (both projects and maintenance) but then moved into quality assurance when regulators started to look more in detail at computer compliance, and subsequently into more of a standards, risk, and assurance role in IT. I think having had that experience and background of having to deliver GxP-validated systems (in my case, an engineering role) really helps you understand the challenges when you move into a quality or assurance role.

I've been working with validation almost all of my career. Validation can seem complex, but I try to make things simpler for people, and often after talking them through the processes, we can usually simplify the approach. I think there is often the view that it is "one size fits all" with validation and its associated complexity and bureaucracy, with mountains of documentation. But when you discover the particular challenge and boil it down to the real risk areas—and fundamentally understand potential areas of patient safety, product quality, and data impact—you can almost always make it much simpler.

What do you see next for your area?

Clearly there is a lot of focus around artificial intelligence and machine learning, and the challenges of dealing with massive amounts of data, and within an emerging regulatory environment for artificial intelligence. From a validation perspective, I think we still need to focus more on critical thinking and computer software assurance (CSA) principles and techniques. What we tried to do with *GAMP® 5 (Second Edition)* was to provide more examples of how to apply true risk-based thinking in practice, and in the context of technological advances, such as cloud computing, blockchain, and AI, and how to leverage information rather than have a documentation-based approach, from software tools, for example.

The other big challenge the industry has is cybersecurity. That is probably the top risk for many companies. The cyber criminals are leveraging the same technology we're using. In a regulated environment, you have to balance the need for control and/or compliance and the ability to protect assets with the need for agility and customer experience.

What advice would you give emerging leaders in the pharmaceutical industry?

If the leader is in IT, they must absolutely try to understand the business and the business processes. At AstraZeneca, we have a program where people are given the opportunity to spend three months working in a different area. Getting that experience early in your career, and expanding your knowledge of the business, is invaluable.

For you, what are the benefits to being an ISPE member?

The biggest benefit is having the opportunity to network with a broad range of people—from other pharmaceutical companies, suppliers, consultants, and even regulators—and hearing different views, perspectives, and approaches. I think hearing those different perspectives is really important; you can always learn from that. It is very valuable that we get to hear the regulatory perspective and have the ability to provide commentary and feedback via ISPE on draft regulations. It has also been good over the years to see how GAMP has expanded its content and relevance beyond its original manufacturing focus to cover all GxP-regulated areas, such as clinical, and continues to develop as new IT technologies emerge.

— Marcy Sanford, ISPE, Publications Coordinator

VOLUNTEER
PROFILE

BRANDI STOCKTON, GAMP® AMERICAS COMMUNITY OF PRACTICE CHAIR

Brandi Stockton is Founder of The Triality Group, LLC, where she provides quality, regulatory, and compliance consulting services for life sciences companies. She has more than 20 years of GxP experience, with a specialization in computer systems quality and data integrity. Brandi joined ISPE in 2014. In addition to being chair of the GAMP Americas Community of Practice, she is a member of the GAMP Global Steering Committee. She is also Co-Lead of the GAMP Global Software Automation and Artificial Intelligence Special Interest Group, leading the team working on an ISPE GAMP Good Practice Guide on artificial intelligence and machine learning, and Vice President of the ISPE Great Lakes Chapter.

How did you become interested in working in the pharmaceutical industry?

I was studying to be a paralegal and you had to find an internship for the last part of the program. Most of the members of my cohort went to law firms. At the time, the Diagnostic and Statistical Manual of Mental Illness (DSM-5) had undergone updates, and articles about mental illness, therapy, and Prozac were all over the news—on the cover of magazines like *Newsweek* and *Time*.

I am from Indiana where Eli Lilly is headquartered. Prozac was their product, and I thought it would be a great place to learn about not only what was happening in the medical field, specifically with the DSM-5, but also mental health generally, and to look at law from a different perspective. I think it was the first time Eli Lilly had someone ask to be a paralegal intern in their legal department.

After graduation, I decided I really wanted to do something that helped people. I worked for a law firm that focused on civil rights and one that focused on immigration for hospital staff. I received a call from Eli Lilly asking me to cover a childbirth leave and spent much of the next 14 years working there in sales and marketing and quality control labs, setting up good manufacturing practice libraries. In between a couple of contracts, I also worked at Riley Children's Hospital and the American Diabetes Association.

What do you enjoy most about your work?

I wear a lot of different hats: overseeing operation strategy, managing client relationships, and providing quality and regulatory consultancy services for life science organizations. I really enjoy being able to bring people together to collaborate and to design teams based on a company's specific needs. I enjoy knowing that what I do truly helps organizations. I like to solve complex problems and help people understand what is possible, like what we are exploring in the artificial intelligence space right now.

What do you see next for your area?

There are great technologies out there and in development. But we, as an industry, have not invested enough time upfront to train and prepare people and we have not always learned from past opportunities. I think organizations are beginning to have a better understanding of the true challenges they face when trying to implement innovative technologies like artificial intelligence and recognizing that they should be seeking advisors and trainers.

In my experience, those that have reached out for external help have been able to more easily and successfully adopt new technologies. I hope we're going to see more and more connections, more collaboration, and sharing of success stories. Because once we develop trust and confidence, have the processes in place, and get the training and upskilling of people right, then we're going to see some truly amazing products and therapies.

What advice would you give emerging leaders in the pharmaceutical industry?

Get involved in something that is a challenge. If you volunteer for something you don't know a lot about, you are going to learn so much more as opposed to volunteering for something you're already an expert in.

Do not undervalue your worth. At ISPE I've seen many emerging leaders who sit on the sidelines and think they don't have anything to contribute right now, but they do. Don't hesitate to raise your hand, speak up, or ask questions. When you ask good questions, others learn as well. Also, it is okay to walk away from opportunities that you are not learning from.

You are already awesome. Don't wait to become something you already are.

For you, what are the benefits to being an ISPE member?

I get to help shape the industry and connect with stakeholders that I might not have met otherwise. You may work in operations, but you have little interaction with regulatory affairs, for instance. At ISPE I get to meet people from all those areas. It is a place to go to interact with those stakeholders in a meaningful way.

— Marcy Sanford, ISPE Publications, Coordinator

ISPE Announces the 2024 Facility of the Year Award Winner

At the 2024 Facility of the Year Award (FOYA) Celebratory Banquet, ISPE announced the 2024 overall FOYA winner: Eli Lilly Kinsale Limited's IE2b project. In addition to winning the overall award, Eli Lilly's IE2b project was recognized as the 2024 Innovation category winner for its innovation in synthetic peptide manufacturing.

Located on the Eli Lilly and Company manufacturing campus in Kinsale, Ireland, the IE2b Peptide Manufacturing Facility is a state-of-the-art complex that represents years of innovation, teamwork, and attention to detail. The facility manufactures crude drug substance synthetic peptides that can be shipped to other sites for final product purification, isolation, and packaging.

In designing the facility, the Eli Lilly team took a step back from the traditional synthetic peptide manufacturing process to evaluate best practices from the world of peptides and beyond. The resulting vision was a first-of-its-kind hybrid active pharmaceutical ingredient (API) synthetic peptide manufacturing platform that could support high-volume production of life-saving peptide medicines at a commercial scale.

"There were more barriers to doing this than anyone could imagine, but we put a group of people together who were thinking big with a bold, can-do attitude. It's amazing to see what can be achieved and has been achieved here," said Darragh McDonagh, Senior Director of Engineering at Eli Lilly Kinsale Limited.

The now active IE2b facility uses a combination of innovative technologies, including a novel hybrid manufacturing platform that significantly increases annual throughput and reduces risks during the peptide manufacturing process. Continuous flow processing and a first-of-its-kind nanofiltration system remove the need for downtime between steps while ensuring more precise control of reagents and materials. Meanwhile, process analytical technology (PAT) lends visibility and control, allowing the team to seamlessly manage stoichiometry to ensure high-efficiency reaction step conversions and yields.

Equally integral to the new manufacturing platform and facility is its digital mandate and material tracking model that marries the flow process with digitization. With this model, facility personnel can determine what raw material inputs are in any process step or item of equipment at any point in time. Together, these features enable a robust, data-rich process control strategy and significantly reduce the traditional time-consuming workload, complexity, and risk of completing these calculations manually.

The emphasis on cross-functional collaboration and risk mitigation, including investing in proven technology and consulting with regulators along the way, paid off for the team behind the project. The facility was finished on schedule, achieved a right-first-time startup, and experienced no significant safety disruptions after over 1.6 million construction hours. A year of operation has revealed the value of high-frequency monitoring, high-quality data, and the ability to control and release batches at an unprecedented rate.

To date, the team estimates IE2b has an annual throughput multiple times higher than traditional peptide production processes. The innovative hybrid manufacturing approach can yield more products with higher quality and less waste. This ultimately brings a more reliable supply of medicines to patients.

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.

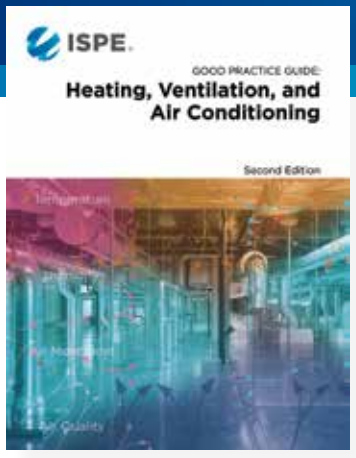
Each year, submissions are accepted from projects worldwide, representing breakthroughs in various disciplines, from automation and integration to the development of medicines for underserved populations. Ultimately, a panel of industry leaders chooses the projects that set the standard to receive a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

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

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

The Need for a New HVAC Good Practice Guide

By Marcy Sanford



Since its original publication in 2009, the *ISPE Good Practice Guide: Heating, Ventilation and Air Conditioning* has been helping engineers design heating, ventilation, and air conditioning (HVAC) systems that meet regulatory compliance while maintaining product safety, worker safety, and comfort.

However, the need for a second edition was evident, as options available to HVAC designers and engineers have evolved due to technological advancements and shifting project pressures. The updates in the second edition reflect these changes, providing readers with a more current perspective on the challenges and resources involved.

"Since the original guide was published, both the technology and guidance on how to implement an HVAC system for the pharmaceutical industry has changed. There is also a need for more efficiency and a push toward decarbonization," said guide co-lead author Josh Williams, Senior Mechanical Engineer, Genesis AEC. "There are new products that are being produced now that didn't exist then, or even five years ago, and new technology sectors that are coming about due to recent advances in cell and gene processing techniques."

"The new guide also reflects new and updated regulations such as Annex 1," said guide co-lead author Christopher Anderson, CPIP, HVAC Engineer, Hikma. "It is a valuable resource if you are looking for answers of where to start when designing an HVAC system or what to do if a problem arises."

Designing HVAC systems for the pharmaceutical industry involves unique considerations. Facilities where medicine and other health-related treatments are manufactured must be exceptionally clean and safe environments to protect both personnel and products.

As a result, HVAC systems in pharmaceutical settings require higher levels of reliability, robustness, design scrutiny, and operational assurance compared to less-stringent applications. Given that HVAC systems can consume a significant portion of the energy used by a facility, their design necessitates a blend of good engineering practice (GEP) and good manufacturing practice (GMP).

"If an HVAC system is not designed properly, there is a significant risk of potential danger to individuals within the facility from product contamination and cross contamination among ingredients which could lead to loss of life-saving products, and discomfort or suboptimal operating conditions for facility workers," Williams said.

"Auditors always want to see well-designed systems," Anderson added. "If you look at FDA 403s there are plenty of examples of companies being cited for HVAC systems that are either not properly qualified or not properly operated. Issues with the HVAC systems can lead to noncompliance with regulations which can affect overall business operations, while a good well-designed system will help your company get through an audit quicker."

This updated guide aims to clarify GMP HVAC issues that are critical to the safety, identity, strength, purity, and quality of pharmaceuticals, biopharmaceuticals, advanced therapy medicinal products, and medical devices, from raw materials to finished products. It covers HVAC control and monitoring requirements and addresses GEP issues related to sustainability, economics, and environmental health and safety. The guide provides best practices for implementing international regulatory and industry guidance, with appendices containing industry examples and templates for the reader's reference.

Written by industry experts with input from members of the ISPE HVAC Community of Practice, additional topics covered in the guide include:

- Energy use and sustainability considerations
- System configurations by facility type
- HVAC and environmental controls and monitoring
- Commissioning, qualification, and quality risk management
- Life cycle documentation, operations, and maintenance

For more information on this and other ISPE Guidance Documents visit, ispe.org/publications/guidance-documents

Marcy Sanford, ISPE, Publications Coordinator

ISPE Foundation: Recent Highlights

By Isabella Stoup

Since our inception, the ISPE Foundation has continually invested in people and helped shape the future of the pharmaceutical industry. We continued this momentum last year and hope you will join us in supporting the workforce of the future in 2025.

ANNUAL GOLF TOURNAMENT

With over 20 sponsors, this year's Annual ISPE Foundation Golf Tournament was a huge success. The event took place on the last day of the 2024 ISPE Annual Meeting & Expo in Orlando, and was time well spent with networking and friendly competition for a great cause. Featuring raffles, games, and an opportunity to "Beat the CEO," multiple participants went home winners.

In total, more than 100 industry professionals gathered on the green to support the ISPE Foundation's greatest needs. This helped advance our mission of fueling global health equity by fostering access to knowledge and nurturing diverse talent. We eagerly anticipate our next tournament, which will take place in Charlotte, North Carolina, alongside the 2025 ISPE Annual Meeting & Expo.

PROFESSIONAL DEVELOPMENT GRANTS

With a generous contribution from the Moderna Foundation to the ISPE Foundation Professional Development Grants program, the ISPE Foundation made strides at the conference by supporting the attendance of 24 students and recent graduates from around the globe.

This program addresses the ongoing shortfall of a diverse and knowledgeable workforce by providing grantees with access to ISPE conferences, where they can grow personally and professionally though a plethora of networking opportunities, educational sessions, workshops, and trainings. After each conference, grantees are awarded a two-year ISPE membership and access to various ISPE trainings so that they can continue to connect with others and build industry knowledge.

Speaking about the grant, recipient Vincent Nguyen stated, "I emerged from the conference with a renewed appreciation for the ISPE Foundation's unwavering commitment to cultivating the next generation of leaders in our field. Engaging with fellow grantees illuminated the organization's pivotal role in nurturing future innovators. The discussions highlighted both the ISPE Foundation and ISPE's extensive focus on professional development through a variety of programs and robust mentorship opportunities. This investment in individual growth is not just beneficial, it is crucial, as it directly correlates to the overall success and sustainability of our industry."

Thanks to a generous contribution from the Moderna Foundation, the ISPE Foundation brought 24 students and recent graduates from around the world to the 2024 ISPE Annual Meeting & Expo.

In 2025, we will continue to provide globally diverse STEM students and Emerging Leaders access to the life-changing opportunities available through the ISPE Foundation Professional Development Grants program.

ACADEMIC SCHOLARSHIPS

The ISPE Foundation is proud to announce the Delaware Valley Chapter Scholarship fund in partnership with the Delaware Valley Chapter of ISPE. Thanks to a USD 60,000 contribution from the Chapter, each year the scholarship fund will provide STEM students in the Chapter's region with scholarships to help cover academic costs. The Delaware Valley Chapter is paving the way for many by supporting their local up-and-coming pharmaceutical professionals throughout every step of their career. We look forward to hearing the stories of the many students who will be supported through this fund.

Please consider a charitable contribution to further the success of the future of our industry to the ISPE Foundation's Scholarships and Grants pillar, which supports both the Professional Development Grants program and academic scholarships. To learn more, please visit ispefoundation.org/donate/scholarships-and-grants

Isabella Stoup, ISPE Foundation, Development Coordinator

Pharmaceutical Engineering

2023 Article of the Year

The article "Comparability Considerations for Cellular and Gene Therapy Products," published in the November/December 2023 issue of *Pharmaceutical Engineering*, has been named the 2023 Roger F. Sherwood Article of the Year. Written by Kathleen Francissen, PhD, Andrew Chang, PhD, Katherine A. Donigan, PhD., Emily C. Hernández, PhD, and Sam Gunter, MPP, the article discusses key considerations for evaluating the comparability of cell and gene therapies when manufacturing processes are altered.

"The article wins the 2023 Article of the Year Award because it thoroughly describes the challenges the industry faces to scale up or out the manufacturing process of complex products like cell and gene therapies, as well as any risk assessment that needs to be done when faced with a change in the manufacturing process or in the materials used. The article is very useful for cell and gene therapy professionals and stakeholders 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: the award recognizes quality and excellence in content by identifying finalists and a single winning article for each publication year.

2023 JUDGING

A subcommittee of the PEC served as judges for the 2023 award competition, reviewing articles and providing assessments on the following criteria:

- Usefulness to ISPE readers
- How the articles improve knowledge of key topics
- Clarity and ease of reading

Roger F. Sherwood Article of the Year PHARMACEUTICAL ENGINEERING

The article is very useful for cell and gene therapy professionals and stakeholders in development and manufacturing.

2023 AWARD FINALISTS

The other articles selected as finalists for the 2023 Roger F. Sherwood Article of the Year were:

- "A Proposal for a Comprehensive Quality Overall Summary" by Roger Nosal, Connie Langer, Beth Kendsersky, Jennifer L. Brown, Megan E. McMahon, and Timothy J.N. Watson, PhD
- "Agile Data-Driven Life Cycle Management for Continuous Manufacturing" by Rui C. Silva, PhD, Rui Almeida, Pedro Ferreira, José Cardoso Menezes, PhD, and Angela Martinho
- "An Evaluation of Postapproval CMC Change Timelines" by Rob Harris, PhD, Meike Vanhooren, Kara Follmann, PhD, Beth Kendsersky, Timothy J.N. Watson, PhD, Melinda Imperati, S. Connor Dennis, PhD, and Roger Nosal
- "New EU AI Regulation and *GAMP® 5*" by Anders Vidstrup
- "Delivering Curative Therapies: Autologous vs. Allogeneic Supply Chains" by Pinar Cicalese, PhD, and Niranjan S. Kulkarni, PhD
- "Design Considerations for Large-Scale Stem Cell Manufacturing" by Daniel L. Swanson, BSChE, MBA, PE, and Christian Estes, PE
- "Environmental Sustainability in Biopharmaceutical Facility Design" by William G. Whitford, Emily Heffernan, PE, and Aoife Kelly

Your Professional Development at the Facilities of the Future Conference

By Mike Martin

The 2025 ISPE Facilities of the Future (FoF) Conference will be held 27–28 January in San Francisco, California, US, and virtually. Mike Martin, the conference's Executive Chair, offers advice and shares what attendees can expect at the upcoming conference.

What are the top three reasons you would tell someone they should attend this conference?

In our work, we often get insulated or isolated. We look at and solve problems the way we have experienced them. This conference will allow you to see how others have solved similar problems, and you will likely find a novel idea that will help you in your work. Attending this conference will help break the insulation and isolation that so many of us experience in our work.

Second, you don't know who you don't know. This conference presents a great opportunity for you to connect with others in industry. You might get a great technical idea from a new colleague. You might get a bit of leadership wisdom from an experienced industry leader. And you might be that source of ideas and wisdom for someone else. Maybe your experience and your wisdom will light the way for another person.

Lastly, we work in a great industry and there are great stories of the impact that we are all having on improving human life. You will find inspiration and energy during the conference that will provide motivation in the often difficult work in which you are engaged.

What are you most looking forward to?

I'm looking forward to the connections and the stories of others. I'm constantly impressed with the work that other people are doing and how that work has helped the world. Conference attendance has always caused that sense of inspiration for me, and I'm looking forward to that experience again.

Any advice for someone to make the most out of the conference?

Our world is full of distractions and urgent requests from work and home. Do your best to connect to the conference and its topics. Listen closely. Submit questions. Dive into discussions at the network breaks. Be present in the "conference moment." You will get the best reward if you can set aside your regular work for a couple of days and focus on your professional development.

The greatest mentors that I have encountered in my career made their own professional development a priority.

Why do you think professional development is important?

Our professional growth drives our career growth. Whether you are an aspiring deep technical consultant or a future business leader, engaging in the idea of lifelong learning is the fuel that your dream needs. Professional development doesn't just happen; it must be owned. The greatest mentors that I have encountered in my career made their own professional development a priority. Own it, and you will be it.

Why did you volunteer to be a conference chair?

After serving as a member of the conference committee, I wanted to use my experience and my connections to create a strong conference that would fuel the professional development of my colleagues. Watching others grow and get excited about their own learning has enhanced my own experience. Serving as a conference chair has multiplied this effect for me.

Why do you enjoy being a member of ISPE?

My entire career has been connected with engineering in the pharmaceutical industry. At the center of my life is a desire to help others and to improve the quality of life for others. ISPE helps me connect to others who have that same passion and who take joy in sharing and helping others grow. The ISPE organization is a brotherhood and sisterhood for likeminded people who want to improve the way life is lived.

About the author

Mike Martin is the President and CEO of ISPE and the ISPE Foundation. Previously he was the CEO of CAI, an engineering consulting company that primarily serves the pharmaceutical industry. He has more than 35 years of experience in the pharmaceutical industry, mostly with a large global pharmaceutical company. He has a variety of experiences in engineering, operational leadership, engineering leadership, and large-scale project management in diverse global settings. Mike has delivered major capital projects in the US, Puerto Rico, China, and Ireland. He is a mechanical engineer with an MBA. He joined ISPE in 2002.

Aseptic Conference Focuses on Technical and Regulatory Issues

By Christa B. Myers

The 2025 ISPE Aseptic Conference will be held 17–18 March in Washington, DC, and virtually. Christa Myers, the Conference Chair, offers advice and shares what attendees can expect at the upcoming event.

Why should someone attend this conference?

The ISPE Aseptic Conference is considered one of the most complete technical and regulatory-focused conferences in the industry because it brings forward case studies, new technologies, and regulators together in rooms to talk about concepts that are key to delivering safe aseptic and sterile products to the industry. The time spent in the training sessions, in the questions and answer sessions, and in the expo hall is high-value time due to the fact that innovation, quality improvements, and cost savings that can be discovered and planned in a matter of two days.

What are you most looking forward to?

There are really two big things that I am looking forward to: The regulatory panel and the industry panel. The ISPE Aseptic Conference is known for the regulatory panel that happens on the second day. Attendees can pose questions to the US Food and Drug Administration (FDA) to answer. Over the years, this session has had great impact on operations companies as they prepare for their regulatory compliance reviews with the US FDA, EMA, and others.

The other item that always delivers incredible technical learnings is the industry panel: it is a highly diverse panel that addresses hot topics for the production of aseptic and sterile products. Each year, the panelists bring more and more depth to the discussion by bringing the newest and most complex issues to the forefront: transfers of sterile materials, training of personnel, ease of changeover, and improvements in operation are all big topics this year.

Any advice for someone to make the most out of the conference?

To make the most out of the conference, my suggestion is that you show up early and attend the Aseptic 101 event on Sunday night before the conference. Attending can help solidify your terminology and allow you to meet students, meet subject matter experts (SMEs) in the industry, and start to create your network of mentors. If it takes a village to raise a child, it takes partnerships across the entire industry to operate and improve aseptic manufacturing.

Why do you think professional development is important?

Professional development is extremely important to maintain current GMP. One of the most dangerous groups in an organization is one that is stagnant and non-improving. Professional development is one of the most important levers to pull to create an involved, empowered, continuous improvement organization. Quality, as per ICH Q10, is not supposed to be a stagnant, controlled environment. It is supposed to be ever-improving and ever-evolving. The US FDA, EMA, and others are calling for more improvements for methods, training, and data management every year. It will take professional development and exposure to committed people with different experiences in order to continue improvement in operations.

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Professional development is extremely important to maintain current GMP.

Why did you volunteer to be a conference chair?

I am a big believer in giving back to the organizations that have served my growth, and I know without a doubt that by serving within ISPE, I gain more than I give—no matter how much I give. The group serving as the Aseptic Conference Planning Committee is one of the most incredible groups of people that you will ever meet. By working with these individuals across the planning year, I learn more and more about the industry, conference planning, and individuals. I gain a great deal from being around them along the way.

Why do you enjoy being a member of ISPE?

ISPE provides an environment that allows for continuous learning. There are ample resources and opportunities to pick up on the leading edge of industry changes and expectations. I utilize discussion forums, *Pharmaceutical Engineering®* magazine, communities of practice, Baseline Guides, and several of the conferences to stay up to date on technological advancements and changes in regulatory expectations.

After many years of investing time and effort into helping ISPE, I have also found that it allows me the time and places to meet new people and build my community. The network of resources becomes highly valuable when obscure questions around operations and regulations occur. It is fantastic to be able to reach out to a community of well-trained people and find the best answer for the situation. Without ISPE, a lot of time could be spent to come up with appropriate answers.

About the author

Christa B. Myers has been in the pharmaceutical industry for over 30 years and is a leader and SME. She frequently speaks on regulatory requirements, operational issues, and what to expect in the future of the industry. She champions approaches that integrate strong project execution and technical solutions. She provides guidance and leadership to clients on how and when to use common or innovative solutions and she continuously promotes the technical growth of people willing to learn more to advance the industry. Christa is on the Steering Committee for the ISPE Community of Practice for Sterile Products Processing, a certified ISPE Instructor of the Sterile Product Processing Baseline guide, and Annex 1, former Chair of ISPE's Women in Pharma® group, and an author of the *ISPE Baseline® Guide: Sterile Product Manufacturing Facilities (Third Edition)*. She was recently awarded an honor as a 2019 Influential Woman in Manufacturing. She joined ISPE in 2007.

Meet the ISPE STAFF

LANEISHA WALKER

Hometown: Houston, Texas

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

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

As Sales Operations Manager, my day is about ensuring everything runs smoothly for the sales team. I analyze sales data to spot trends and find ways to improve our processes. Whether it is making changes to our customer relationship management system, managing forecasts, or working with different stakeholders to execute contract deliverables, I focus on removing obstacles so that the sales team can focus on selling.

What do you love about your job?

What I love most about my job is the multiplicity of tasks and the opportunity to make a real impact. Every day is different, whether I am solving problems, fine-tuning processes, or working with clients across the globe. I love the challenge of collaborating with other teams and stakeholders, figuring out how to make things more efficient, and seeing those efforts pay off in actual results. The global aspect is especially exciting. It is rewarding to build relationships and see how our solutions can make a difference for clients and partners worldwide.

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

Outside of work, I enjoy spending time with my family, especially my 11-year-old son. It is a joy to watch him explore new interests and discover the world.

In Memoriam: Tony Trill, a GAMP Legend

by Charlie Wakeham

It is a rare and wonderful legacy to have substantially improved your chosen industry and to have bestowed a name on an initiative that, 30 years later, has become synonymous with best practice. This article celebrates both these pivotal achievements of Anthony (Tony) Trill, who passed in 2024.

Tony Trill started his career in the life sciences working for a series of global multinational pharmaceutical companies. After 18 years, he went on to become an inspector with the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom—a position he held for 24 years. He was responsible for Good Manufacturing Practices (GMP) standards and inspection guidelines for computerized systems.

"His personal support was invaluable in helping me set up the ISPE Supplier Forum with UK government funding in the mid-1990s. This was later incorporated into the main GAMP organization that we know today. I am sure he will be deeply missed by all who remember working with him. I have a vivid memory of his smile, and dry humor with that twinkle in his eye. So long, Tony. Thanks for the memories along our shared GAMP journey." — Guy Wingate, PhD, VP & Compliance Officer (retired), GlaxoSmithKline

He represented the MHRA during the redrafting of the European Union's "EudraLex, Volume 4: EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use. Annex 11: Computerised Systems," specifically chapter 4. Trill also led the Pharmaceutical Inspection Convention (PIC/S) Expert Circle for Computerized Systems, the group that developed the "PIC/S Good Practices for Computerized Systems in Regulated 'GxP' Environments" used by regulatory authorities around the world for inspecting computerized systems [1].

At a meeting at Keele University in April 1989, Trill led a discussion on the new regulatory expectations for computerized systems [2]. This meeting was attended by Tony Margetts of Zeneca Pharmaceuticals (now AstraZeneca), who would go on to form the UK Pharmaceutical Industry Computer Systems Validation Forum (UK PICSVF), with Trill as a member. The UK PICSVF leveraged

"I got a lot of earache from the management about involving Tony [in the original PICSVF], such as, 'Why are you talking to the inspectors? They are the enemy!' I am glad I did. Tony was very helpful in the early days as we discussed the type of guidance required by the industry." — Anthony (Tony) Margetts, PhD, Principal Consultant, Factorytalk Co., LTD

Zeneca's internal Validation Management document (VMAN) to create a first draft guidance on computerized systems.

At the time of the first draft's launch in London in March 1994, Trill suggested a new name for the initiative, replacing the unpronounceable PICSVF with "GAMP," then an acronym for Good Automated Manufacturing Practices. The team became the GAMP Forum, and ultimately Tony served on GAMP Steering Committees at both the European and global levels for many years. Although the ISPE Community of Practice and its many high-level good practice guides still use the name GAMP Tony coined, it is no longer an acronym.

"He was a great GAMP supporter and instrumental in getting the regulators' attention. His contribution to GAMP's global acceptance was enormous. He was very dedicated to the GAMP cause and a very valuable colleague with numerous contributions not only supporting GAMP, but more widely ISPE. He will always be fondly remembered by those who worked with him." — David Selby, PhD, General Site Manager, Glaxo Wellcome Operations, Barnard Castle (retired)

"Tony was a huge advocate for GAMP. It's a big loss for our GAMP community and the industry as a whole. Tony was truly a member of the GAMP hall of fame." — Michael Rutherford, 2024 Interim President and CEO of ISPE

Tony contributed extensively as both author and reviewer in every edition of the GAMP guides up to and including *ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems Guide for Validation of Automated Systems* [3]. His long-term dedication to GAMP was hugely instrumental in both its success and its recognition by the regulatory agencies across Europe. His involvement set the precedent for other agencies such as the US Food and Drug Administration (FDA) and Therapeutic Goods Administration of Australia to interface closely with GAMP. A strong advocate of the practical execution of GAMP principles, Trill was a regular conference speaker at ISPE events, sharing his in-depth knowledge and unique approach to slide animations and presenting.

Trill's retirement from MHRA in 2009 did not reduce his passion for improvement in the pharmaceutical industry, and he continued to support GAMP and monitor ongoing developments. In 2023, he joined the GAMP Special Interest Group Global Software Automation and Artificial Intelligence, and attended the ISPE GAMP CoP UK Forum event in April 2024 just months prior to his passing.

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Charlie Wakeham is Director of WakeUp to Quality and Chair of the ISPE GAMP Global Community of Practice Steering Committee.

HARNESSING AI/ML TECHNOLOGY for the CQV Life Cycle

By Luca Mussati, Sakthi SSA, and Archa Vermani, PhD

Technology is advancing at an extraordinary rate. Industries are gaining the benefits of automation and artificial intelligence (AI). The life sciences industry is no exception [1–2]. As technological developments continue to reform the way industries run, the integration of AI and machine learning (ML) technologies are redefining the traditional approach to commissioning, qualification, and validation (CQV) in pharmaceutical manufacturing.

As the life sciences industry becomes increasingly more regulated, complex, and dynamic, so does the CQV life cycle. Traditional CQV approaches often fall short, but implementing AI/ML can revolutionize the CQV life cycle.

CQV requires huge efforts with the expectation to turn over equipment, systems, and facilities promptly for manufacturing use. This involves generating deliverables that will be used throughout the life cycle of the equipment or system within a stringent timeframe. The speed at which deliverables are generated carries the potential risk of human error during document generation, execution, and turnover management.

AI/ ML technologies are appearing as a notable change in CQV by streamlining, automating, and optimizing various stages of the life cycle [3]. Machine learning applications can significantly accelerate the CQV phase by automating the analysis of validation data, finding trends, and predicting potential issues and anomalies that may go unnoticed by human observers.

ML algorithms can adapt to changing conditions, improving the agility of validation processes. This predictive capability allows for proactive decision-making, reducing the risk of unexpected issues [4]. As we navigate through this combination of innovation and established industry practices, the influence of AI/ML offers a better future, where efficiency and compliance combine to optimize the CQV processes.

By harnessing the power of AI/ML, CQV has the potential to overcome challenges in data analysis, automated workflow creation, anomaly detection, risk assessment, and predictive modelling. The technology is superior in optimizing the commissioning process, integrating different systems and components enabling predictive maintenance, and supporting decision-making processes—all in a much faster and compliant manner as compared to humans. It can improve overall efficiency, accuracy, and effectiveness of the CQV process.

The transformation of the CQV life cycle using AI/ ML technology will streamline and accelerate the overall process leading to improved outcomes significantly enhancing productivity, reducing timelines, and boosting overall effectiveness of the project life cycle.

BACKGROUND

CQV serves as a foundation within the pharmaceutical manufacturing industry to ensure the integrity and reliability of the manufacturing processes. “Commissioning” is the process of ensuring that a system or facility is designed, installed, tested, and is operating according to its intended specifications which accounts for Good Engineering Practices (GEP). “Qualification” is the process of verifying and documenting that equipment, systems, and processes are installed and operate correctly and consistently within established specifications. “Validation” is a process of establishing documented evidence that a system or process consistently produces results meeting predetermined specifications and quality attributes. Qualification and validation account for Good Manufacturing Practices (GMP).

This article explores how AI/ML technologies can transform the CQV life cycle. As technological developments continue to reform the way industries operate, the integration of AI/ML technologies pave the way to redefine the traditional approach to CQV.

AI/ML technologies account for some noteworthy changes in CQV by streamlining, automating, and optimizing stages throughout the CQV life cycle [3]. ML applications can significantly accelerate the CQV phase by automating the analysis of validation data, finding trends, and predicting potential issues, and anomalies that may go unnoticed by human observers. ML algorithms can adapt to changing conditions, improving the agility of validation processes. This predictive capability allows for proactive decision-making, reducing the risk of unexpected issues [4]. As we navigate through this combination of innovation and industry established practices, the influence of AI/ML offers a better future where efficiency and compliance seamlessly coexist to redefine the excellence in the CQV process.

REVOLUTIONIZING THE CQV LIFE CYCLE

The pharmaceutical industry is experiencing a paradigm shift with the integration of AI/ML into the CQV life cycle. CQV is a critical step in ensuring that manufacturing processes and systems are

properly designed, implemented, and maintained to produce safe and effective products. Conventional CQV methods often involve manual testing and extensive documentation, leading to extended timelines, inefficiencies, and potential errors. Because AI/ML technologies can evaluate vast amounts of data quickly and find patterns or variances, they help in identifying and addressing gaps that might be missed by operators and reviewers.

Another crucial benefit of implementing AI/ML in CQV is enhanced data analysis capabilities by enabling real-time monitoring of process and equipment. This is done by collecting data from various sources such as sensors or electronic records. This allows for proactive identification of issues before they turn into a costly downtime [3]. By harnessing the power of AI/ML technology, we can address challenges, making the workflow smarter, more adaptive, and efficient. Therefore, the usage of AI/ML technology in the CQV life cycle offers significant benefits and enhances overall efficiency and effectiveness.

Because AI/ML technologies can evaluate vast amounts of data quickly and find patterns or variances, they help in identifying and addressing gaps that might be missed by operators and reviewers.

Translating Need to Blueprint

Recognizing the need for AI/ML technology enables the design and implementation of solutions. As a prerequisite, a complete understanding of the process, equipment, supply chain, and data quality compliance are essential to having a strong design basis [5]. A multidisciplinary approach with domain expertise is required for collective functioning, tailoring unique solutions and mitigating challenges [6].

Because data and records in the pharmaceutical industry are highly critical, sensitive, and subjected to regulatory reviews, selection of advanced sensors, instruments and field devices that can integrate and exchange data at all levels (i.e., from field level to supervisory or management level) are required. This is because data plays a crucial role for real-time monitoring and control at different stages of the process [3]. Other considerations, such as robust data storage systems and infrastructure, are crucial for managing large data volumes from equipment and systems. Additionally, a clear data management strategy is essential to maintain data reliability and integrity [3, 6].

When integrating or implementing AI/ML technology with existing infrastructure, several factors should be evaluated for further prospects [4]. These include understanding the current level of automation, layers of data exchange, integration with different systems (e.g., laboratory information management systems and inventory management systems) and the capability of other information technology/operational technology (IT/OT) infrastructure to adapt this change. If the current infrastructure can support a change, then the data from various levels, equipment, and IT/OT infrastructure can be collated according to the requirement to create a data source for an AI/ML model.

If the existing field devices' infrastructure does not support the AI/ML implementation, the level of change required can be assessed with a detailed implementation strategy. The level of change could range from upgrading the existing instruments at the field level to operational requirement changes at the supervisory/management level. This depends on the current condition and the expected state proposed to achieve using AI/ML technology [2].

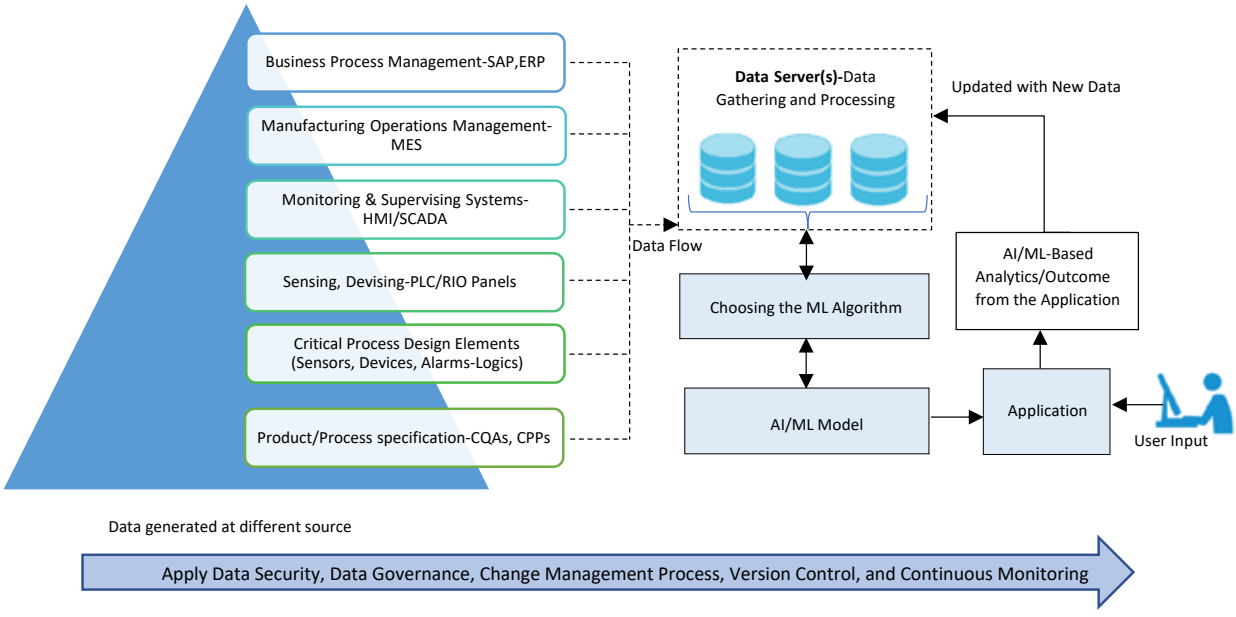
Intelligent sensors and Internet of Things devices when integrated with AI/ML algorithms, can check system performance in real time, facilitating early detection of deviations from the established limits [3, 5]. This enhances traceability and ensures that every step is documented and validated in real time, thereby improving the equipment occupancy. With automation and controls in place, we can achieve consistent results while the operators can be assigned to focus on improving more complex aspects of validation. In addition to improving efficiency and accuracy, incorporating AI/ML into the CQV life cycle promotes compliance with regulatory standards. Automated systems can ensure that all necessary documentation is complete while adhering to industry guidelines throughout every stage of validation.

Since "data" are key influencers in revolutionizing the AI/ML technology in CQV life cycle, adopting quality by design principles in data collection processes right from the process developmental stage is essential to the success of implementation [7]. Hence, focus should be on designing a scalable system with horizontal and vertical integration of the processes to handle large amounts of data, which can be utilized for data analysis, predictions, and more [3, 4, 8] throughout the life cycle. This further enhances the quality, safety, and efficiency of the process. A clear, strategic approach that combines factors is essential for successful implementation of AI/ML in this highly regulated industry [6, 7]. These factors include deep understanding of process/equipment, infrastructure/technical possibilities, technology advancement, cross-functional domain expertise, and regulatory principles.

A HIERARCHICAL APPROACH TO CQV LIFE CYCLE USING AI/ML

The hierarchical approach to CQV life cycle using AI/ML, as shown in Figure 1, employs the automation pyramid, which is followed by the manufacturing plant [5]. The data and/or signals collected

Figure 1: Hierarchical approach to the CQV life cycle using AI/ML.



from the equipment or system in field via sensors and actuators are processed into actionable insights as per the requirements specified at each level [6]. Huge amounts of data are continuously generated by sensors, controllers, and recorders in the equipment or system.

Data from these flows into the data server and/or historian, which serves as an input for AI/ML algorithm and model development. The AI/ML model processes this data, which contains massive amounts of information. This helps in analytics, performance evaluation, modeling, and decision-making. It also provides new opportunities to find patterns and solve difficult conditions that have never been seen or correlated before [8]. This enhances the process and improvement actions during the CQV phase and routine operations.

To improve the overall process or system, it is important to focus on the individual steps or unit operations. Changes made at the individual level will affect the performance of the overall manufacturing process and/or system. To have effective control and efficient process, it is important to have correct, reliable, and quality data at each step [5]. This helps in thorough analysis and develops an understanding of correlation of how changes made to unit operation or system parameters are contributing to the improvement of overall system and manufacturing processes. Hence, the key to effectively manage and improve a system lies in having quality data at each step of the process that serves as an input to AI/ML models.

Over time, the AI/ML model will be acquired with more data, and it will continue to improve its understanding based on the data feedback loop. The ability of the AI/ML model to iteratively learn over time depends on the type of approach and algorithm used. This ability to learn from vast data and experience and improvise the process over time is the key characteristic of the AI/ML system. It also enables the model to handle complex tasks and provide predictive suggestions at a much faster pace than human beings. Such applications of AI, ML, robotics, and other advanced technologies to perform CQV activities that are traditionally carried out by human operators is called autonomous CQV [6].

Autonomous CQV refers to a modern approach within the pharmaceutical industry that involves technologies like AI/ML, robotics, and automation streamlining and enhancing the CQV processes. This includes document generation, execution, data collection, analysis, and reporting carried out with minimal human intervention. The aim is to minimize human error, increase productivity, and ensure compliance with regulatory standards throughout the life cycle of the equipment or system.

APPLICATION AND BENEFITS OF AI/ML

Implementation of autonomous CQV by integrating AI/ML can have a significant impact in improving process knowledge, efficiency, accuracy, and compliance. Some applications are depicted in Figure 2.

Piping and Instrumentation Drawing (P&ID) with AI/ML

Requalifying existing brownfield projects can pose challenges, particularly when P&ID walkdowns are hindered by a lack of accurate "as-built" P&IDs. The traditional method of creating or updating P&IDs relies on manual labor when draftspersons physically navigate the site to convert observations into computer-aided design (CAD) drawings. However, this manual approach often leads to inaccuracies, delays in the requalification processes, and high associated costs. Introduction of the AI/ML-based robot revolutionizes P&ID development with its advanced technology.

Figure 2: Some applications of AI/ML in the CQV life cycle.

During site walkdowns, these robots employ cameras or scanners to collect reliable 3D data, ensuring precise documentation that mirrors actual site conditions. An AI/ML-based robot can be deployed even in confined spaces. It offers a comprehensive 360-degree view through remote access, driving significant time and cost savings by streamlining data collection and reducing manual efforts, thus minimizing rework during project execution.

The in-built 3D scanners in the robot produce detailed point cloud data that can be imported into various CAD software. Moreover, this technology enhances design visualization, aids decision-making, facilitates conflict resolution, and ensures regulatory compliance, ultimately saving time, resources, and promoting sustainability by minimizing waste.

AI-Enhanced Installation Verification

AI revolutionizes equipment installation verification during CQV processes. Through automated image analysis, AI algorithms meticulously scrutinize the actual site condition/installation images or videos by comparing them against predefined trained data sources like installation manuals or videos and CAD models. This help detect errors such as misalignment or missing components. Real-time monitoring powered by AI ensures prompt anomaly detection by analyzing sensor data during installation, enabling swift corrective actions.

AI-driven computer vision systems visually inspect installations, capturing errors like loose connections or damaged components, with remarkable precision. Predictive analytics models forecast potential issues based on historical data, facilitating proactive measures to prevent errors or malfunctions. AI streamlines the compliance process by automating verification, reducing human error, and enhancing accuracy, efficiency, and safety in equipment installation processes, ensuring strict adherence to standards.

Resource Optimization

ML algorithms can analyze project requirements, resource availability, and historical data to optimize resource allocation throughout the CQV process. By accurately matching personnel, equipment, and materials to specific tasks and projects, organizations can minimize idle time, improve resource utilization, and reduce costs, thereby enhancing schedule efficiency and cost-effectiveness [3, 5].

Project Risk Prediction and Mitigation

AI/ML techniques can analyze project data to anticipate risks and forecast their probability and consequences on schedule and expenses. These algorithms evaluate project risks by scrutinizing factors like project complexity, resource availability, and regulatory demands. Through proactive identification and resolution of risks, organizations can implement mitigation strategies, leading to smoother execution, reduced rework, and reducing the possibility of schedule extensions [9, 10].

Predictive Project Cost Analysis for CQV Activities

AI/ML-based predictive modeling techniques forecast CQV project costs by considering factors like project size, complexity, regulations, and location. These models learn from past data, update predictions with new information, and continuously improve accuracy over time. They analyze feedback and performance metrics to refine predictions and adapt to changing requirements and market conditions. AI can conduct scenario analysis to evaluate the impact

of different project variables on overall costs. By simulating various scenarios and adjusting parameters such as project scope, timeline, or resource allocation, AI can help project stakeholders make informed decisions to optimize cost-effectiveness.

Automated Test Script Generation

AI/ML algorithms can analyze historical data from previous validation projects and provide inputs to generate optimized test scripts automatically. These scripts can be tailored to specific equipment or systems, reducing the time and effort required to develop testing protocols from scratch. By automating this process, organizations can significantly accelerate the validation timeline and minimize associated costs.

ML models further aid in adjusting test cases as the system evolves, ensuring ongoing relevance of validation efforts. Adhering to change management processes is crucial for maintaining system integrity, including assessing and implementing ML model modifications effectively. Monitoring the updated model's performance ensures it meets expectations, with robust version control and tracking mechanisms ensuring transparency and accountability throughout the equipment life cycle [4, 6].

Real-Time Monitoring and Decision Support

AI-driven analytics platforms can analyze large volumes of data in real time from validation activities, providing insights into validation processes, equipment performance, and potential issues, which supports CQV teams in their decision-making. For example, these AI-driven systems can flag deviations from expected performance metrics, recommend corrective actions, or alert personnel to potential compliance issues. By leveraging these insights, decision-makers can identify areas for optimization, anticipate challenges, and make informed decisions to streamline the CQV process [3, 4].

Automated Document Management and Reporting

AI-powered document management systems use natural language processing algorithms to automate various tasks related to document organization, retrieval, traceability, and review of CQV documentation. These systems can extract relevant information from test results, equipment logs, and other sources to generate reports automatically. By automating these tasks, manual work is reduced, human errors are minimized, and the documentation process is accelerated. Ultimately, this streamlines the CQV process and improves the overall audit trail.

Predictive Maintenance

AI/ML can be employed in predictive maintenance to predict failures before they occur by analyzing sensor data and historical maintenance records. By implementing predictive maintenance strategies, organizations can minimize unplanned downtime, prevent costly equipment failures, and optimize maintenance calibration schedules to maintain the validated state of the equipment and systems. This leads to significant cost and time savings.

Training and Knowledge Management

AI/ML models can adapt the learning path based on the individual's progress, performance, and interest for a customized experience. Integrating virtual reality and augmented reality technologies can create realistic and immersive training experiences [9]. AI-powered chatbots can provide immediate assistance and respond to queries related to training materials. This leads to organizational growth and more efficient, personalized, and adaptive learning experiences for employees [6].

CHALLENGES AND CONSIDERATIONS

AI/ML in CQV processes can offer numerous benefits, but it also presents several challenges and considerations [5, 6, 10, 13].

Challenges

Data quality and quantity

AI/ML models require large volumes of high-quality data to train effectively. Obtaining sufficient historical data for CQV processes may be challenging.

Data integrity and security

Ensuring the integrity and security of data used for AI/ML models is critical. This is particularly true in regulated industries where data integrity is paramount for compliance with regulations, such as the US FDA's 21 CFR Part 11 [14]. Maintaining data integrity throughout the CQV life cycle is essential.

Data privacy

Stringent security measures are crucial when handling sensitive data in CQV processes to prevent inadvertent disclosure. It also safeguards organization, equipment, and personnel information, which prevents privacy breaches of information used in AI/ML models. Compliance with data privacy regulations preserves data utility for AI/ML model training, and robust data sharing agreements with third-party vendors prevent unauthorized access.

Model interpretability and explainability

AI/ML models often operate as black boxes, making it difficult to understand the reasoning behind their decisions. In regulated industries, it's crucial to ensure that CQV processes are transparent and understandable, which may require using interpretable ML models for developing methods to explain model predictions.

Regulatory compliance

Adhering to regulatory requirements is a fundamental aspect of CQV processes. Introducing AI/ML into these processes requires careful consideration of regulatory guidelines and standards, such as the US Food and Drug Administration (FDA)'s validation requirements for computerized systems and the European Medicines Agency's guidelines [11].

Validation of AI/ML models

Validating AI/ML models for use in CQV processes requires

demonstrating their reliability, accuracy, and consistency. Establishing validation protocols and methodologies specific to AI/ML models can be challenging due to their complexity and dynamic nature.

Considerations

Data selection and management practices

Establish a comprehensive strategy to collect important data, making sure all necessary sources are identified and available to train and validate the AI/ML models effectively. Data sources can be diverse and tailored to meet the specific needs, each presenting unique considerations. These sources range from structured to unstructured data.

Risk assessment

Conducting a comprehensive risk assessment is essential to identify potential risks associated with the use of AI/ML in CQV processes. Understanding these risks allows organizations to implement appropriate risk mitigation strategies and controls.

Expertise and training

Building internal expertise in AI/ML and providing training for personnel involved in CQV processes are critical considerations. Organizations may need to invest in training programs to ensure staff have the necessary skills to develop, implement, and maintain AI/ML-based systems.

Collaboration and stakeholder engagement

Collaboration between cross-functional teams, including quality, manufacturing, IT, engineering, and regulatory affairs, is essential for successful integration of AI/ML into CQV processes. Engaging stakeholders throughout the process helps ensure alignment with organizational goals and regulatory requirements.

Continuous improvement and monitoring

Implementing AI/ML in CQV processes requires a commitment to continuous improvement and monitoring. Organizations should establish mechanisms to monitor model performance, address issues as they arise, and incorporate feedback to refine and optimize AI/ML systems over time.

Ethical and social considerations

Ethical considerations, such as bias in AI algorithms and the potential impact on workforce dynamics, should be carefully evaluated. Organizations must ensure that AI/ML systems are developed, deployed, and maintained in a responsible manner, aligning with ethical principles and societal values, as defined in ISO 42001 standard [12].

AI-powered document management systems use natural language processing algorithms to automate various tasks related to document organization, retrieval, traceability, and review of CQV documentation.

Data governance

Privacy by design is crucial in AI/ML system development. Principles like data minimization and purpose limitation reduce privacy risks by ensuring that only necessary data is collected. Transparent communication about data practices fosters trust and accountability. Obtaining informed consent from users is essential. Robust data encryption and access controls enhance data security. By adopting privacy-enhancing technologies, organizations can mitigate privacy risks and build trust in their AI/ML initiatives. By tackling these challenges, organizations can use AI/ML to improve efficiency, accuracy, and compliance in CQV processes while reducing risks and ensuring regulatory adherence.

CONCLUSION

AI/ML revolutionizes the CQV life cycle, boosting efficiency, accuracy, and innovation to meet evolving demands effectively. Traditional approaches fall short, leading to inefficiencies and higher costs. Applications like AI-/ML-enabled resource optimization, P&ID development, installation verification, and automated test script generation drive productivity, quality, and cost-effectiveness improvements by optimizing resource allocation. Proactive risk prediction and mitigation prevent delays or failures, and predictive project cost analysis aids resource allocation. Real-time monitoring offers actionable insights for compliance and performance optimization.

Automated document management and reporting ensures regulatory compliance, and predictive maintenance maximizes equipment uptime. AI/ML-driven training fosters continuous learning, empowering organizations to thrive in a dynamic environment. Yet challenges such as data integrity, security, organizational readiness, and cultural adaptation persist. Collaboration among industry stakeholders, regulatory bodies, and technology providers are vital to surmounting these obstacles and unlocking AI/ML's full potential in CQV. Organizations must stay vigilant, adaptable, and dedicated to driving positive change as they embark on this transformative journey. With AI/ML, we can revolutionize the CQV life cycle, attaining unparalleled efficiency, agility, and quality while shaping future industry standards and innovation.

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THE ROLE OF AI AND ML in Efficiency and Innovation

By Chloe Lang and Timo Schmidberger, PhD

The integration of artificial intelligence (AI) and machine learning (ML) into bioprocess development represents a rapid shift in the way discovery, development, optimization, and production of biological products are approached.

Bioprocesses, which involve the use of living cells or enzymes to manufacture drugs, vaccines, and other high-value compounds, are inherently complex and data-intensive. Other fields in pharma, such as drug discovery or medical devices, seem to be leading the implementation of AI/ML methods. There is currently a list of 950 AI- and ML-enabled devices provided by the US Food and Drug Administration (FDA) [1]. The increased awareness and accessibility of AI and ML technologies also offers unprecedented opportunities to harness this complexity and turn vast amounts of data into actionable insights that can then lead to more efficient and cost-effective bioprocesses.

ALGORITHM GUIDANCE

It is important to acknowledge that many of these concepts, especially for ML, are currently established in industry as chemometric or multivariate data analysis (MVDA) techniques [2]. MVDA is a discipline within ML that can use both supervised and nonsupervised algorithms. Although these techniques have been used for many years, it does not mean they are less relevant or less effective than other AI/ML algorithms.

In fact, for certain applications and use cases, they provide advantages in explainability. Choosing which algorithm to use should be assessed on a case-by-case basis and based on factors such as the available data, complexity of the problem, and risk assessment. There is existing guidance in place from the United States Pharmacopeia [3], FDA [4], and European Medicines Agency (EMA) [5] providing clear starting points for further utilization of AI/ML applications.

HEALTH AUTHORITIES

A variety of health authorities have been proactive in encouraging the adoption of AI and ML. For example, in 2014, the US FDA Center for Drug Evaluation and Research (CDER) established the Emerging Technology Program to work collaboratively with companies to support the use of advanced manufacturing. In 2019, the FDA asked for feedback on the then proposed regulatory framework for modifications to the "Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device Action Plan," which was eventually published in January 2021. The US FDA also published the guideline "Good Machine Learning Practice for Medical Device Development: Guiding Principles," published in October 2021 [6].

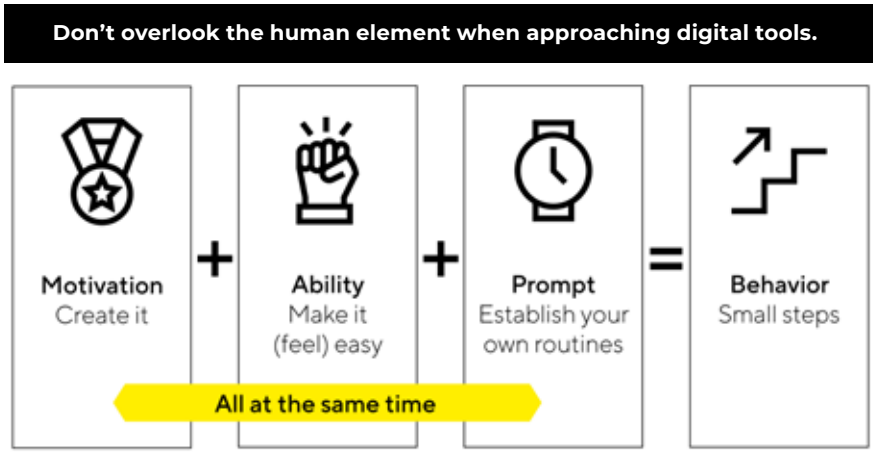
The benefits of using AI/ML are also acknowledged by the US FDA [7] and the EMA [8] to establish better guidance for AI/ML use in the whole development journey from molecule selection to drug product. International organizations, including the International Society for Pharmaceutical Engineering (ISPE) and BioPhorum, are publishing more holistic guidelines on requirements and steps to build AI/ML-based models in a regulated environment [9–12].

CHALLENGES

However, the successful implementation of AI and ML in bioprocess development is not without its challenges. One significant hurdle is the tendency for data scientists to work in silos, focusing on narrow aspects of the data science domain without a holistic view of the entire system. Typically, that means they are focused more on the data itself or the algorithms and less on the process science. Siloed thinking can limit the potential of AI and ML applications, as the true power of these technologies lies in their ability to integrate and analyze data across different stages and scales of the bioprocess. Developing AI expertise internally in organizations is a complex task. Creating the diverse teams needed to spearhead this change is a challenge. Moreover, the adoption of AI is often carried out in isolation. Typically, AI-driven processes are executed separately from the core scientific and daily operations, leading to a situation where AI applications are not seamlessly integrated with standard daily procedures [13].

The field of process science increasingly intersects with data science, as practitioners leverage advanced large language model (LLM) tools, such as ChatGPT, to develop AI and ML solutions tailored to specific problems. Although this approach seems to effectively democratize data analysis, enabling broader access and utilization, it also carries inherent risks, such as the suitability of the information utilized to produce an output from LLMs. Plus, process scientists may lack a comprehensive understanding of the underlying methodologies.

Figure 1: The benefits of AI/ML algorithms should encompass key aspects to enhance end user engagement.



Gaps in expertise, which can lead to misguided decisions, were identified as a current industry challenge in a 2022 report issued by the Association of the British Pharmaceutical Industry (ABPI). "This is a huge growth area for healthcare data science, and demand currently outstrips supply. A significant proportion of strong data science candidates have limited life sciences experience, and this must be taught on the job for them to become effective," said a respondent of a survey cited in the report [14].

AN INTEGRATED APPROACH

To fully leverage AI and ML in bioprocess development, it is crucial for AI/ML tools to be adopted with a more integrated approach. This means moving beyond the confines of specific domains of data science and making the tools accessible to interdisciplinary teams, including bioprocess engineers and other domain experts. By doing so, data scientists would ensure that AI/ML tools (models and algorithms) they develop are working as intended, and the bioprocess scientists would ensure the tool can be utilized in a meaningful and actionable way.

Teams involved in such projects will vary depending on the application and complexity. It is important to identify the stakeholders, which could include engineers developing a specific application to improve a control strategy, automate reporting, or create a feedback model incorporating a large amount of data (e.g., from research and development, production, or supply chain) to identify learnings that can be leveraged for the next product creation.

The integration of such tools and applications can have impacts at all levels of operations of an organization, which should be carefully considered to ensure time and resources are deployed in an effective manner. Generating data or applications does not always generate more value, and creating a company culture to embrace changes and adopt new tools or workflows can be challenging.

The Fogg Behavior Model [15] highlights this challenge and recommends key aspects for consideration. Introducing new tools or workflow requires introducing a new behavior to someone's workday. Behavior is driven by three ingredients working simultaneously: motivation, ability, and prompts (see Figure 1). This is important because you could have the best tool in the world, but if there is no motivation to use it, it is overly complicated for the end user, or there are no prompts or routine to incorporate its use, it will bring no value. Considering potential hindrances early in the process and encouraging necessary behavior changes, can lead to smooth rollouts that meet milestones..

Incorporating data analytics into the toolkit of process scientists and connecting company-specific applications from data scientists within their organization is a step toward creating more interdisciplinary collaboration. This article introduces the concept of working with both commercially available software platforms combined with open source to facilitate the rapid configuration of data analytic workflows. These workflows, crafted by data scientists, are intended for seamless adoption and utilization by process scientists, thereby bridging the gap between complex data analysis and practical application in the field.

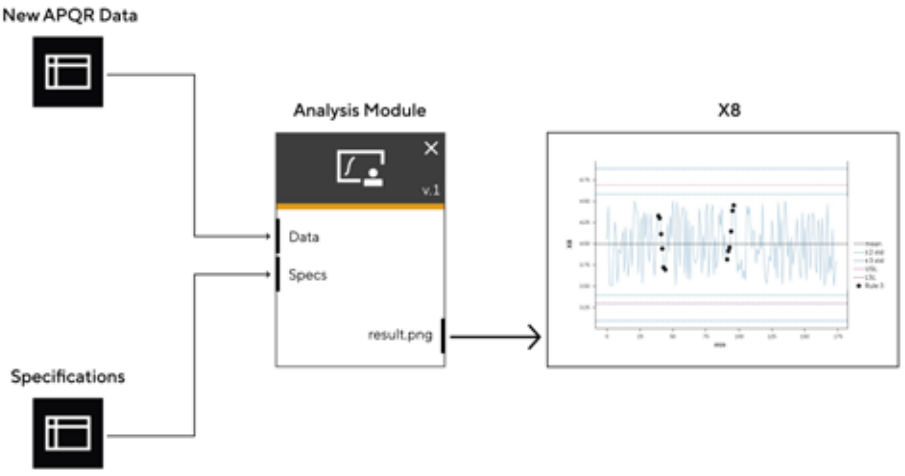
CASE I: QUALITY AND PERFORMANCE ASSESSMENT

A safe and efficacious product is the overarching goal for both manufacturers and authorities. To enable this goal, many guidelines and regulations are implemented and supported by internal company procedures. One central requirement for commercial products according to "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry," updated by the FDA in 2020, is that "Regular quality-reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually…" [16].

Accordingly, this guidance may be systematically documented within the annual product quality review (APQR).

A standard workflow would involve a cross-functional team comprising a process scientist, an analytical expert from quality control (QC), or a manufacturing specialist who is responsible

Figure 2: This figure demonstrates workflow to assess data in terms of APQR. Breaches of Nelson Rules are indicated by black dots.



for aggregating data from various sources. This collated data is then submitted to the statistical department where professionals conduct statistical analyses in accordance with the company's standard operating procedures. The completed analyses would then be shared with the originating department. Subsequently, the manufacturing or QC team undertakes a thorough review and interpretation of the outcomes to ensure compliance with quality standards to inform continuous improvement initiatives or open investigations for noncompliance findings.

So how can that workflow be simplified so that the analysis can be done directly by manufacturing or the QC department? A workflow builder offers exactly this possibility to generate workflows to execute repetitive tasks and deploy the workflow to colleagues. How would a workflow be created? First, a data connection to the well-defined and qualified source data needs to be established. This should enable a secure connection to all relevant data (such as defined operating ranges, critical quality attributes [CQAs], and performance indicators) and increase the overall data integrity compliance for the application.

The statistical department is tasked with developing a module tailored for the statistical analysis and reporting of this data. It is crucial to ensure data format is standardized to facilitate seamless processing. A common methodology to support this analysis are Nelson Rules which are typically applied to control charts to identify datapoints that fall outside of specification as well as trends that are against random noise.

In this example, the statistical analysis would be to apply four different Nelson Rules to data (see Figure 2). Data points that violate one or more Nelson Rules should be flagged because they need to be investigated. The statistical model developed should encompass not only the statistical evaluation but also a results component. In the context of our example, this would include a graphical representation, such as a plot, to identify instances where Nelson Rules may have been breached.

The foremost purpose of the APQR is to quickly assess if the production process was under control or within specified limits in the previous reporting period. In the workflow presented previously, the manufacturing or QC employee requests to run the workflow which would be followed by a generated report. Another large advantage to automating reporting workflows is compliance with regulatory standards, as the steps in the process will require clear traceability to qualified systems. This reduces the possibility for manual errors and ensures compliance through automation and data integrity standards, ultimately resulting in higher operation efficiency from more effective resource utilization.

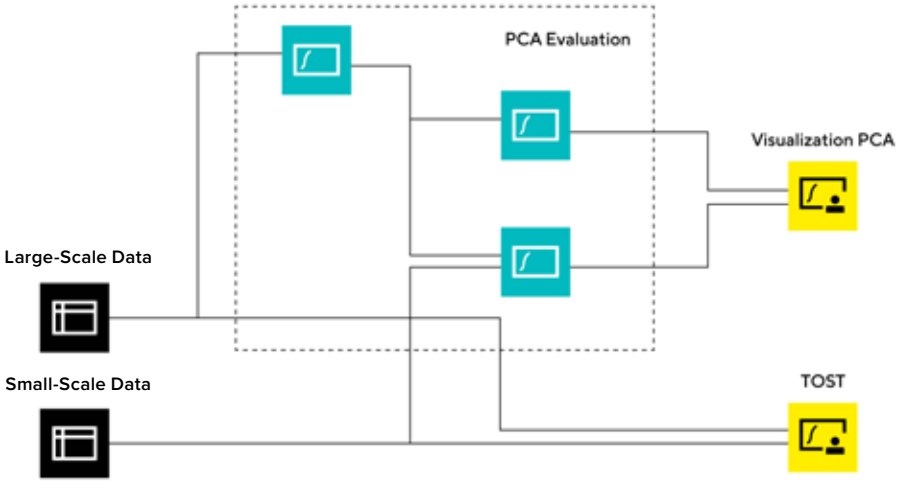
There are a variety of further use cases that can benefit from automated workflows, for example, the APQR result can be used for continuous process improvement. To achieve this, a second workflow can be designed for the manufacturing science and technology (MSAT) department using the very same data and data connection, but running data mining tools or digital twin kind of models to identify potential improvements to the process.

This is just one example of an application where robotic process automation (RPA) can be utilized. RPA has significant potential in the pharmaceutical industry, with benefits in both operational and compliance aspects. RPA can remove repetitive tasks, speed up decision-making, reduce the risk of errors in data collection and analysis, and expedite reporting to enable process optimization [17].

CASE 2: SCALE COMPARABILITY

The second use case has a slightly more complex structure but is equally important. Scaling in bioprocessing is a critical phase in the development and commercialization of biopharmaceutical products. It involves the careful transition of biological processes from the laboratory bench or pilot scale to larger-scale production systems. This step is essential for meeting the demand for therapeutic proteins, vaccines, and other biologics. On the other hand, there might be cases where scaling processes downward is

Figure 3: Workflow for scale comparison



needed to support troubleshooting or life cycle management of commercial processes.

Effective scaling is not merely a matter of increasing the size of the bioreactors and other equipment. It requires a deep understanding of the biological systems involved and the impact of scale on process parameters, such as mixing, oxygen transfer, and nutrient supply. Although physical properties like tip speed can be easily calculated, others such as the volumetric mass transfer coefficient (kLa) are more challenging to derive. One fundamental problem remains within bioprocessing—just because most physical considerations are similar across scales, the biological response of the living cells in the reactor might be different.

At the end of any scaling, it is important to assess if the scaling was successful or not, meaning the biological performance, including the quality of the product, is equivalent across scales. Typically, different statistical methods are used to check if quality is preserved across scales or that certain key performance indicators (KPIs) are met. The toolbox of statistical tools applied ranks from univariate comparison such as t-tests or equivalence testing to multivariate approaches to assess time series data.

Scaling is required for most commercially manufactured products, meaning that scale comparison and assessment is a repetitive task. Here again a generic workflow can be of great value to standardize and automate the evaluation. Scaling can be applied in both directions (scale-up and -down). This example, highlighted in Figure 3, shows the workflow for scale-down.

Workflows should address whether scales are equivalent. The first step is to decide what methods are needed to show the scale comparability. In this case, a principal component analysis PCA for time series data and two one-sided t-tests (TOST) for key performance indicators (KPIs) and critical quality attributes (CQAs) were selected. Typically, the data science department could then start to program the relevant modules. An alternative approach to build the models or statistical evaluation could be the use of self-programming tools like ChatGPT (which will be highlighted in case 3). Once the statistical modules are finished, the workflow can be assembled and tested. The workflow consists of three parts: data connection (black boxes in Figure 3), MVDA (teal-colored boxes in Figure 3), and assessment of results (yellow boxes in Figure 3).

The outcome of the workflow is shown in Figure 4. Figure 4A depicts the result of the PCA analysis of the time series data. First, the large-scale data is compressed using PCA. As a next step, the distance to origin for each large-scale batch is determined and two standard deviation 2SD limits calculated (shaded blue area). In the plot shown, the small-scale data is compared to limits based on the large-scale data. Batch 56 and batch 57 are outside and are displayed in detail in the plot next. Figure 4B shows boxplots of the harvest titer as a representation of a KPI for both large-scale and small-scale data. The more KPIs and CQAs, the more boxplots need to be generated. Figure 4C shows the result of the TOST for the harvest titer. The more KPIs and CQAs, the more TOSTs need to be performed.

As a final step, the process scientist would simply update the small-scale data and run the process. The first step in improving the small-scale model is in understanding if the scales are comparable. It requires the right tool set and an understanding of how to use data analytics for the assessment. A workflow like the one shown in this section can help get to a reliable assessment quicker to the right end user (the bioprocess subject matter expert [SME]). In case the evaluation demonstrated comparability, no further actions are needed other than the summary of the results and a formal report on small-scale validation.

However, in case the result of the workflow is nonequivalence between the scales, additional work needs to be done. Typically, the next stage is to understand what the scaling parameter culprit for nonequivalence could be across scale. Solving this problem could lead to another workflow that uses AI/ML with a high degree of explainability. There are examples demonstrating how design of

Figure 4: Results of Scale Comparison: A) PCA analysis results of the time series data B) Boxplots of the harvest titer, representing a KPI for both large-scale and small-scale C) TOST results for the harvest titer

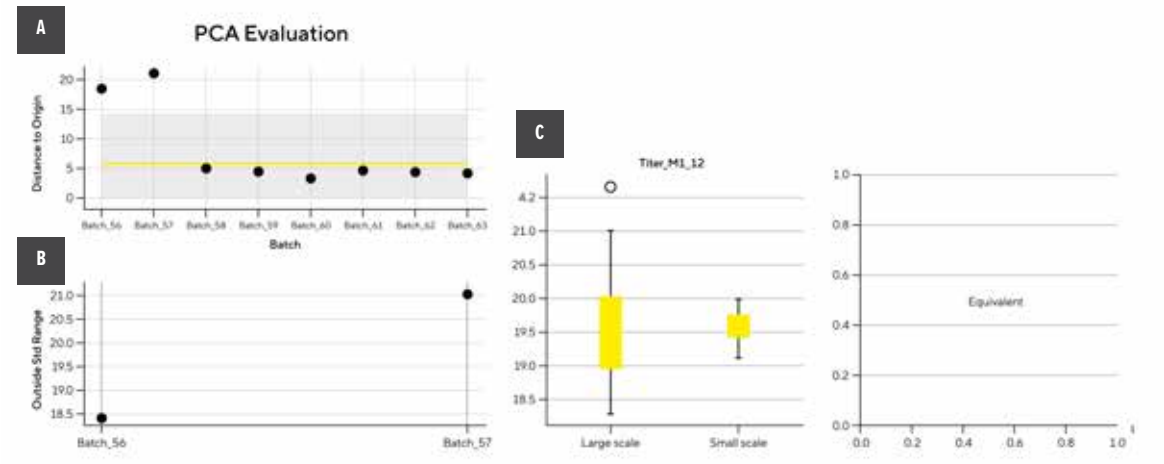
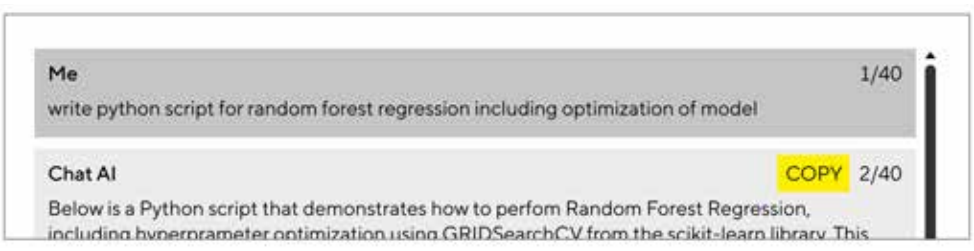


Figure 5: ChatAI workflow



experiment in combination with MVDA can help identify possible adjustments for more comparable biological performance between scales [18].

Another approach to detect and understand nonequivalence can be the use of hybrid models (also called digital twins). Both techniques can be based on AI/ML algorithms trying to represent the biological behavior within a process model. These models can be used to investigate different process settings and assess which ones will result to more comparable process [19]. Once a new scale-down approach was found (independent of the algorithm used), the equivalence testing (e.g., with the workflow shown here) must be repeated.

CASE 3: DATA MINING TOOL BASED ON RANDOM FOREST

A common and important task in bioprocess development is mining historical data to utilize existing knowledge to establish a starting point for any new bioprocessing development activities. Typically, and following quality by design (QbD) principles, this activity starts with risk assessment to identify the most important parameters to be investigated in design of experiment (DOE) approaches.

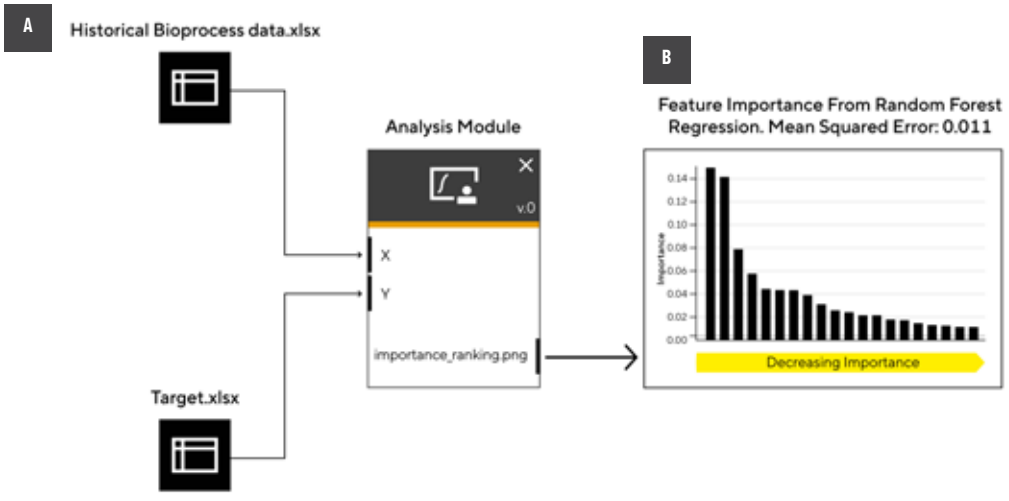
Part of the risk assessment involves looking over dozens or more data spreadsheets to identify trends and behaviors. However, looking over the historical data set can be a complex and time-consuming exercise and if not done properly, there is the risk of overlooking important parameters and starting the development journey from the wrong starting point. Powerful data mining tools such as principal component analysis or random forest can be helpful tools to identify trends and patterns in data; however, due to the limited expertise of process scientists to create these models, these techniques are not routinely utlized.

To provide the process scientist with a summary of the most important and influential parameters as a starting point for follow-up work and to reduce the time required to analyze dozens of data sheets, a random forest algorithm can be implemented. For this example, a random forest algorithm to identify the strongest influencing parameter(s) on the harvest titer of this bioprocess is required.

In the third use case, we want to demonstrate how problem-solving can be boosted by using chatbots for the programming task. In our case, the script's development timeline was reduced from several hours to less than 5 minutes. The process scientist used an internal company AI chatbot (see Figure 5) to develop a robust method with model optimization and feature extraction.

The resulting Python script contained the data import interface, a grid search for testing key parameters for the random forest, and a graphical output to visualize and rank the most important

Figure 6: Result data mining with random forest.



parameters. The resulting script was then embedded in an envelope script to be uploaded into a workflow builder.

Next the different building blocks are assembled, as indicated in Figure 6A. Figure 6B shows the top 20 variables in decreasing order of importance. This would be the basis for process science to identify which parameters to address first for bioprocess development.

This same data mining strategy can be reused or shared with colleagues for the next new product or target assessment and only the respective input files need to be exchanged. It should be noted that the output of the models and reliability of the data can only be as good as the data input. Data mining remains a crucial tool to set a solid foundation for any further development activity right from the start. This solid foundation not only helps the SME profoundly understand the dependencies with the process but opens more opportunities like DOEs, digital twin development, or further (self)-learning algorithms as the process matures.

TYING IT ALL TOGETHER

The ultimate value in the implementation of AI and ML to create efficiency and drive innovation will come with full connectivity and utilization of data created across the entire value chain. For this to be realized, the importance of well-structured, digitized, compliant, and accessible data should not be underestimated. The three use cases outlined previously could also bring greater value to an organization if they were approached in a broader, holistic way. Case 1 highlighted the use of RPA that can be used for compiling data, automating workflows, and reporting. Case 2 highlighted the use of cross-scale analysis, and Case 3 highlighted the use of data mining.

Combining these techniques and applications builds towards a future vision of fully integrated systems and processes that streamline product development, submission documents, process control settings, and operational information. This integration allows manufacturing protocols to be informed by real-time data, enables RPA reporting for batch comparisons, and consolidates relevant data for real-time release. Additionally, it could track market trends for informed production decisions, creating a feedback loop that supports future product development through data mining.

CONCLUSION

The integration of AI and ML methodologies is increasingly revolutionizing operational processes, enhancing efficiency, and expediting decision-making. This technological advancement holds the promise of accelerating the delivery of superior-quality pharmaceuticals to patients, thereby improving healthcare outcomes.

Despite the transformative potential of AI/ML techniques, they are not without their challenges. To begin with, there is the requirement for a well-structured and unified database to enable effective contextualization and analysis of data. The proper application of these technologies is paramount to avoid misuse and to ensure the integrity of the outcomes they produce.

The risk of misuse of AI/ML increases with chatbots for coding, as it offers the possibility to generate complex codes without really understanding the principles or even pitfalls of the approach chosen. But a profound comprehension of the underlying principles of the employed AI/ML methodologies is essential, as is a thorough understanding of their development and validation processes. This ensures that the results yielded are not only reliable, but also safe for drawing conclusions.

A common obstacle in the implementation of AI/ML solutions is the knowledge gap between data scientists and domain experts. Data scientists may lack the specialized expertise required to interpret results within a particular domain, whereas domain experts may not possess the technical expertise to construct and evaluate AI/ML models.

The proposed strategy aims to bridge this divide by fostering a symbiotic relationship between data scientists and domain experts. By designing and testing specific AI/ML workflows,

data scientists can tailor these tools for use by domain experts. This collaborative model not only ensures that workflows are user-friendly and domain-specific, but also encourages ongoing cooperation throughout the initial scope definition phase. Such a partnership is instrumental in aligning the technical capabilities of AI/ML with the nuanced requirements of domain expertise, ultimately leading to more effective and innovative solutions.

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ARTIFICIAL INTELLIGENCE in Drug Target Discovery

By Toni Manzono and William Whitford

The intersection of artificial intelligence (AI) and drug development has ushered in a transformative era, revolutionizing the way researchers approach biomarker/target identification, drug/target interactions, and drug-like molecule design. Rooted in an interdisciplinary fusion of computer science, statistics, and biology, AI in the life sciences seeks to unravel intricate biological phenomena through systematic assimilation, analysis, and interpretation of expansive and diverse datasets [1].

The convergence of AI with pharmaceutical sciences holds unprecedented potential from drug target discovery to the safety of drug administration [2]. For example, researchers recently employed graph neural networks to predict antibiotic activity and cytotoxicity for more than 12 million compounds. Using explainable graph algorithms, they then identified substructure-based rationales for compounds with high predicted antibiotic activity and low predicted cytotoxicity. Following empirical testing, they identified a candidate that evades substantial resistance and is selective against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE) [3].

AI AND THE DRUG LIFE CYCLE

A synergistic relationship between AI and the drug life cycle, including drug target (DT) discovery, will make it possible to streamline therapeutic interventions. It will also pave the way for personalized, patient-centric healthcare approaches. In this article, we delve into the multifaceted potential of AI in revolutionizing one aspect of computer-aided drug design (CADD): AI-enabled DT discovery systems. This includes an outline of the key advancements, challenges, and ethical considerations that underlie this burgeoning frontier [4].

The potential of AI in drug research and development remains substantial, yet its sluggish rate of integration is a cause for concern. This reluctance stems from such factors as entrenched practices and risk aversion within the conservative pharmaceutical industry. However, the hesitancy to fully embrace AI-powered DT development systems may lead to missed opportunities for prospective entity identification, enhanced candidate precision, personalized treatments, and streamlined therapeutic interventions.

As this technology advances, the disparity between the capabilities offered by AI-driven techniques and the status quo may widen, with classical techniques potentially placing patients at a disadvantage by delaying the implementation of more efficient therapy development and delivery strategies.

AI SAFETY AND EFFICIENCY

Recognizing the transformative potential of AI in healthcare, regulators have displayed a proactive stance in ensuring the safety, efficacy, and ethical use of AI-driven technologies in medicine [5]. Thus, it is evident that regulators are playing a constructive role in fostering the integration of AI, and it is other factors within the industry that warrant deeper consideration. Governing and standards bodies are working to ensure the safety, efficacy, and quality of products employing AI within the life cycle framework of *ISPE GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)*[6]. Examples of this include recent work of the Council of the European Union (EU) [7–9], International Organization for Standardization/International Electrotechnical Commission (ISO/IEC) [10], and The US Food and Drug Administration's Center for Drug Evaluation and Research [11–13] call for an urgent modernization of the pharmaceutical industry [14].

AI provides efficiency and entirely new capabilities in analyzing the rapidly increasing type and amount of biological and chemical data employed in identifying potential DTs. It promises to revolutionize the analysis of laboratory data as well as the mining of research publications and digital libraries in the discovery and characterization of biomolecules or pathways associated with disease [15–16] (see Table 1) [17].

Although there are metrics, such as F1 scoring [18], available to report on the efficiency of AI in a particular application, it is hard to overview this in DT discovery. AI-enabled systems and their individual implementations are improving so rapidly that reporting on speed or precision at any one time point is of little value. Also, AI is incredibly powerful in some tasks and very weak in others, so applying AI where it is strong is an important factor in its performance. Nevertheless, the speed and accuracy of AI in facial recognition is a good example of its potential in discovering physicochemical moieties practical in the modulation of a disease phenotype.

Table 1: Examples of public data sources for target identification [17].

Type	Source	Description
Life sciences publications	PubMed	More than 36 million citations of biomedical literature from MEDLINE, science journals, and online books
	PubTator	Web system providing automatic annotations of biomedical concepts using PubMed abstracts and PMC full-length articles
(Small) molecules	ChEMBL	Bioactive drug-like small molecules: containing 2D structures, calculated properties, and abstracted bioactivities
	HMDB	The Human Metabolome Database (HMDB) contains detailed information about small molecule metabolites
	PubChem	World's largest collection of open chemical information. Search by name, molecular formula, structure, and other
Pathways	Reactome	A curated resource of core systems, pathways, and reactions in human biology
	WikiPathways	Provides an open and public collection of pathway maps created and curated by the community in a wiki-like style
Ontologies	Mondo	A semi-automatically constructed ontology that merges in multiple disease resources in a harmonized ontology
Genes	Cellosaurus	A knowledge resource on cell lines. It attempts to describe all cell lines used in biomedical research and production
	ClinVar	An open archive of reports on the relationships between human variations and phenotypes, with supporting evidence
	Ensembl	Provides a centralized resource for researchers studying human genomes and other vertebrates and model organisms
	NCBI Gene	Gene-specific information on genomes completely sequenced, in active research, or scheduled for analysis
Proteins	IUPHAR Compendium	Details molecular, biophysical, and pharma properties of e.g., mammalian ion and cyclic nucleotide-modulated channels
	String	A comprehensive database from sources of known and predicted, physical and functional protein-protein interplay
	UniProt	The central hub for the collection of functional information on proteins, with accurate, consistent, and rich annotation
Drug development information	Drug Central	Info on active ingredient chemicals, pharmaceutical products, drug mode of action, indications, and pharmacologic action
	Open Targets	Platform that builds and scores target-disease associations and annotations for target identification and prioritization

AI-driven tools process and analyze highly structured data from multiple sources, such as analytical instrumentation, instrumentation tables, and human-generated data. But what could possibly be the most amazing aspect of AI-driven data analysis, is its ability to process unstructured data, such as raw text from articles and clinical notes, complex spectral data from analytics, and nucleic acid or gene expression sequences and profiles. In DT development, automating data analysis with AI can lead to a level of efficiency that has never before seen in life sciences research.

AI algorithms contribute to the identification and validation of potential drug targets with unprecedented efficiency, beginning with accelerating traditional approaches to DT discovery design. AI improves the wet-lab affinity measurement and comparative profiling approaches employing chemogenomic libraries using high-throughput techniques to rapidly screen thousands of possibilities. However, AI has revolutionized data-mining-driven approaches in 1) multiomic gene-disease association methods by analyzing multiple types of biological data (omics), and 2) computational structure-based approaches examining docking and pharmacophores. These latter approaches rely heavily on diverse biological datasets (see Table 1) [17].

AI's power expedites the selection of promising therapeutic modes and specific candidates. It also enhances the precision of subsequent drug delivery strategies. Addressing the interconnected nature of therapeutic mode, specific candidate properties, and delivery strategy accelerates the development process, mitigates risks, and advances the paradigm of precision medicine in the pharmaceutical domain.

THERAPY TARGETS: AN EVOLVING DISCIPLINE

A therapy target is a molecule or system in the body directly associated with a particular disease that can be modulated by a therapy. Target identification is increasingly important in therapy discovery following recent innovations in assay and experimental technologies. For example, in computational structure-based drug design (SBDD), the constitution of new pharmaceutical agents follows the 3D structures of biological targets. By understanding the structure of a target molecule at the molecular level, ligands are proposed that can interact with the target in a way that may modulate its function.

Some drugs, such as aspirin, operate through an irreversible covalent modification of the target. However, DTs typically involve the therapeutic active ligand and biological target (usually protein) molecular docking. Once bound, small molecule ligands either inhibit the binding of other ligands or allosterically adjust the target's conformational ensemble.

Investigating these more common, supramolecular (non-ionic/covalent binding) interactions between biological molecules can reveal important bindings, signaling pathways, critical nodes, or chemical reaction catalyzers in disease-related networks. The list of specific systems supporting such potential targets is growing (see Table 2) and all are now integral in the field of DT discovery.

Common pharmacodynamics of the interactions between a drug and its biological target typically involve receptors, enzymes, or ion channels. However, other therapeutic approaches involve the discovery of targets as well. Identification of a defective gene is a form of target discovery prerequisite to gene editing or

Table 2: Biological systems supporting therapeutic target identification.

Protein-protein interaction (PPI)	Small molecules or biologics can be designed to interfere with specific protein-protein interactions to disrupt disease-related pathways.
Molecule docking	Docking studies use computational techniques to predict how molecules, such as a drug and protein, will interact at the atomic level.
Chemical reactions' catalyzers	Catalysts, such as enzymes, can be targeted to modulate metabolic pathways. Enzyme inhibitors or activators can regulate these reactions.
G protein-coupled receptors (GPCRs)	GPCRs are involved in numerous physiological processes. Drugs targeting GPCRs can modulate these processes to therapeutic effect.
Ion channels	Drugs targeting the proteins in ion channels can regulate the flow of ions across cell membranes, influencing electrical signaling.
Nucleic acids	Drugs that target DNA or RNA can inhibit replication in pathogens or to modify cellular gene expression in therapeutic applications.
Receptor tyrosine kinases (RTKs)	RTKs are cell surface receptors that can be targeted by drugs to inhibit or stimulate cell signaling influencing e.g., cell division.
Transporter proteins	Drugs designed to interact with membrane transporters can modulate the uptake of specific compounds to a therapeutic effect.
Ligand-gated ion channels	Receptors involved in fast synaptic transmission in the nervous system can be targeted to produce drugs like anaesthetics and anti-epileptics.
Structural proteins	Genetic disorders can cause abnormalities in structural proteins. Drugs or gene therapies can stabilize or modify them or their function.
Signalling pathways	Rather than targeting individual proteins, some drugs aim to modulate an entire biochemical cascade of events known as a signalling pathway.
Epigenetic targets	Epigenetic modifications are genetic alterations regulating gene expression not due to changes in DNA sequence.

Table 3: AI functions employed in therapeutic target discovery.

Causality detection	Discovers unknown interactions by identifying dependent and/or independent variables, as well as hidden dependencies.
Data comparison	Compares simultaneous and parallel data from multiple active moieties or components in both time-series and event data sets.
Dimensional reduction	Dimensional reduction transforms a number of possibly correlated variables into a smaller number of uncorrelated variables, simplifying complexity while retaining patterns.
Dimensional analysis	The analysis of the relationships between different objects by identifying their essential features and tracking these dimensions as it places new data in the appropriate dimension.
Pattern recognition	Identifying specific behaviors or motifs over large amounts of data. By establishing a smaller dataset as a model, it finds similar patterns along the full sequence of information.
Target prediction	This is the process of calculating the most suitable values for target variables based on inputs from the modeled predictor parameters.
Clustering and classification	Both supervised and unsupervised algorithms reveal groups in datasets by calculating distances in a multidimensional space.

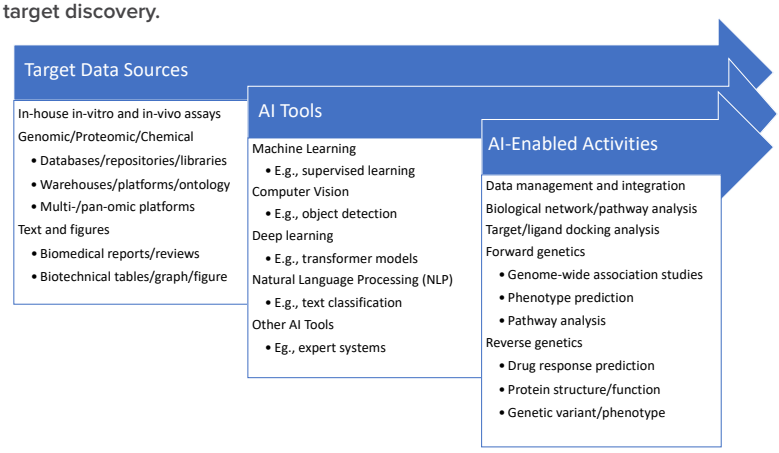
gene replacement therapies. For example, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene are therapeutic targets in patients with cystic fibrosis [19]. The primary therapy approach here is not the use of a drug ligand, but to introduce a functional copy of the CFTR gene into patients' cells.

The 3D structure of a protein is often required in DT identification. Conventional techniques have resulted in such virtual libraries of the 3D structure of proteins as the open-source Protein Data Bank [20]. This comprehensive virtual repository provides 3D structural data of large biological molecules such as proteins and nucleic acids [21]. When the target proteins' 3D structures are unavailable, computational methods such as comparative or homology modeling [22], threading, and ab initio (from first principles) modeling [23–24] have been successful in determining the structures of proteins from their sequences (see Tables 1–3).

Ab initio protein modeling is a computational approach used to predict the three-dimensional structure of a protein based solely on its amino acid sequence and the physical principles governing protein folding. For example, the deep learning–based AlphaFold employs neural networks in a type of machine learning (ML) to perform such modeling, and its source code is freely available [26].

Although by some measurements AlphaFold predictions are remarkably accurate, some note that they do not account for the presence of ambient ligands, ions, covalent modifications, or environmental conditions. In fact, Paul Adams, Associate Laboratory Director for Biosciences at Berkeley Lab, recently remarked, "However, if a researcher wants to study ligand docking for SBDD, there is no substitute for experimental data that provides a higher confidence in amino-acid side chain conformation" [27].

Figure 1: AI enabled drug target discovery.



Ligand sampling is a computational method to predict and optimize the binding affinity and specificity between drugs and targets. It explores the conformational space of a ligand from its pharmacophore to identify energetically favorable interactions within the target protein. Many software packages are now available to support either systematic or stochastic ligand sampling approaches.

Unintended pharmacology or "off-target" effects are often caused by a drug interacting with proteins or receptors other than its intended target. These side effects or adverse drug reactions can now be analyzed via AI-enabled meta-analysis of the candidate therapy's published primary and cross-reactivity. This analysis can be used to map a drug's overall biological activity and targets—suggesting comprehensive physiological effects and clinical outcomes.

Through exhaustive analysis of both research literature and clinical diagnostic data, AI deepens understandings of demographic and individual patient biology. In personalized, or precision, medicines such analysis can help to identify DTs (this includes beyond universal and subpopulation-specific groups to individual patients). In supporting the repurposing of approved medications for use in other indications, ML algorithms perceive patterns in existing medication-related biological data and link them to even targets of unrelated disease [28–29].

PROGRESSION OF COMPUTER-ASSISTED TARGET IDENTIFICATION

Software valuable in pharmaceutical target discovery has been developed since the 1970s: Many locally developed open- and closed-source pipelines, libraries, plugins, web resources, methods, algorithms, software, and user interfaces have been created. These include products providing for the analysis, storage, and interpretation of biological data. Support of evolving fields like computational biology is provided by a number of available programs, including software and tools for sequence analysis (BLAST [30]), structural biology (PyMOL [31]), genome annotation (Artemis [32]), next-gen sequencing (HISAT2 [33]), proteomics (MaxQuant [34]), and cheminformatics (RDKit [35]).

Software supporting molecular mechanics modeling and computer-assisted organic synthesis are used in organic chemistry to design and predict both small and large molecule reactions. It can include the supramolecular chemistries important in many target bindings [36]. In support of them, databases of commercially available starting materials provide practical data for target discovery experimentation [25, 37].

Statistical methods have long been used to identify patterns in data from a DT candidate's measured genotypic or phenotypic properties as compared to the ideal properties. Results of such searches indicate genes, gene products, or bodily systems as potential therapeutic targets. Examples of early work in this field include genome-wide association studies (GWAS). Their aim is to identify associations of genotypes with phenotypes by testing for differences in the allele frequency of genetic variants between individuals who are related but differ phenotypically [38]. A commonly stated goal for GWAS is to use the identified associations to provide a starting point for investigating potential therapeutic interventions.

AI IN TARGET DISCOVERY AND ANALYSIS

A tremendous amount and type of data is generated in analyzing the multiple physicochemical and biological systems associated with discovering a candidate biomarker and pursuing its correlation with disease. Similar data aids in the identification of novel therapeutic targets—in particular, disease. This is done by predicting the ligandability of specific regions, as well as in discovering new targets for existing drugs.

In target discovery, analysis, and validation, three distinct and significant steps now appear:

- AI-assisted governance of data from research experiments, libraries, and crowd-sourced databases of compounds, polynucleotides, and proteins
- AI-assisted organization and harmonization of candidate target and ligand structural classification, relationships, and labeling (e.g., 0D–3D)
- Application of AI methods in preclinical studies (see Figure 1).

Target ligand discovery and characterization increasingly involves a combination of experimental and computational approaches. These approaches require interdisciplinary collaboration between chemists, biologists, pharmacologists, and data professionals. Examples include the actionable conclusions now provided by AI in multiomic studies [39].

The number of analytical approaches employing tools like AI-empowered high-throughput screening (HTS) and high-content analysis (HCA) is large and growing. HTS allows researchers to rapidly screen thousands of compounds against a candidate biological target (e.g., a protein or cellular pathway) and reveal which responds to treatment with a particular compound. For example, affinity-based methods can be used to isolate and confirm a candidate target that interacts with the bioactive compounds.

HCA can collect data simultaneously on such multiple cellular parameters as cell morphology, protein expression, and subcellular localization. AI supports analysis of this multiparametric approach to generate phenotypic profiles correlating with disease states or treatment responses. AI-supported HCA enables the analysis of dynamic processes within cells, in a real-time, high-throughput manner, revealing candidate biomarkers or targets actively involved in disease states or drug responses.

HTS provides a broad initial screen to identify targets of interest, whereas HCA provides detailed, contextual information about the activity of a therapy on cellular processes, which helps identify candidate biomarkers and targets [40]. For example, Kupczyk et al. used supervised machine and deep learning models to calculate mathematical scores from training databases to create the nodes of the neural networks. The results were then used as a reference to organize the HCA data of the experimental set into groups called classes or classifiers. [41].

ML was the first AI tool applied to predicting target–ligand interactions. However, deep neural networks have been shown to outperform both traditional physics-based and knowledge-based ML models. For example, the PotentialNet family of graph convolutions has demonstrated power in predicting the binding affinity of targets/ligands [42].

AI ALGORITHMS

We are seeing such AI algorithms playing a pivotal role in the discovery and analysis of potential DTs. Their proficiency in handling vast and varied datasets, discerning intricate patterns, and generating precise classifications or forecasts revolutionizes traditional, human-dependent approaches [43]. This transformation empowers researchers with rapid, robust, and statistically unbiased systems (managed by expert AI methodologies) for identifying and assessing potential targets, ushering in a new era of efficiency and accuracy in drug research. Examples of AI algorithms employed in target discovery and analysis within the pharmaceutical industry include support vector machines (SVMs) [44], random forests [45], and neural networks [46]. These demonstrate significant promise in enhancing the selection and evaluation of potential DTs (see Table 3). A summary of algorithms and areas in which they can assist are given next.

Computational Docking and Virtual Screening

AutoDock Suite is a growing collection of computational docking and virtual screening methods used in the exploration of the basic mechanisms of biomolecular structure and function that has proven to be powerful in structure-based drug discovery. Over the years, it has been constantly improved and modified to add new functionalities and features.

The latest version of the AutoDock engine is AutoDock-GPU [47]. GPU architectures employing deep learning applications now benefit from new processor types, such as Tensor Core Units. In fact, a method to improve execution time of a core function of AutoDock-GPU by leveraging modern Tensor Core Units has been proposed [48].

In Silico Modeling

Comprehensive in silico techniques using ML and deep learning algorithms model properties, activities, and interactions for potential disease modulating effects. These include bodily components, such as tissues, cell and vesicle surfaces, organelles, blood, and interstitial fluids. The power of this was demonstrated by Insilico Medicine in a phase II clinical trial of its AI-discovered drug, INS018055 [49].

Multivariate Analysis

Automated and high-throughput techniques provide measurement of several distinct variables in thousands of unique experimental samples. Variables in biological systems are typically related to various degrees, and so the enormous data sets are multiparametric and sometimes of high dimensionality. However, for historic reasons, they have not always been analyzed as such. Accurate results are ultimately dependent on multivariate analysis (MVA) [43, 50].

MVA examines the relationships between multiple variables, which can be challenging using traditional statistical methods. AI-enabled MVA reveals the specific relationships, dependencies, interactions, and feedback within these complex and dynamic biological systems. It provides needed approaches to detect and model numerous interconnected factors to provide an accurate interpretation of complex realities. Supported by power computing and cloud capabilities, AI approaches empowered by MVA provide timely predictions, understandings, outliers, pattern recognition, and recommendations.

Examples of this power in currently available drug discovery tools include an open-access ML program called ConPLex. Developed by researchers at MIT, ConPLex predicts DT interactions. It requires only the sequences of the system's proteins and simple descriptions of the candidate drugs to provide a sequence-based prediction of DT interactions [51].

Network-Based Sampling

AI-Bind is an AI model that combines network-based sampling with unsupervised pre-training to improve binding predictions for novel proteins and chemical ligands. It is a deep learning DT combination identification algorithm with promise in drug discovery [52]. In 2018, Öztürk et al. proposed the first deep learning model for predicting binding affinity between drugs and targets. DeepDTA was a good start, and it has inspired a number of deep learning–based programs, including WideDTA [53] and DeepAffinity [54].

Data Resource Searching

Searching compound-target bioactivity data resources can be difficult due to non-standardized and heterogeneous assay types, variability in analytical measurements, and distinct methods for data organization and storage, for molecular structure and motif depiction, and for labels, descriptors, and other terminology. An open-data web platform, DT Commons, features tools to assist in crowd-sourced compound-target bioactivity data annotation, standardization, curation, and intra-resource integration [55].

Recently, powerful commercially available resources have appeared to support the ingestion and integration of varied datasets for use by AI-enabled processing. ONTOFORCE's DISQOVER is one such platform. It integrates public, private, and licensed datasets to provide a single interface with linked data for optimized data exploration and search [56].

In Silico Screening

In the field of chemoinformatics, neural networks have been used for in silico screening through chemical modeling for years. We are now seeing that, based on further application of AI techniques, it is promising much more powerful analyses. This includes employing virtual libraries representing a much larger chemical space [57–58].

Property Prediction

ML models can now predict the properties of new compounds in CADD. This is done by employing both measured features of the chemical and purely theoretical descriptors derived from its chemical graph (a graph theoretical representation of a molecule) or 3D structure data [59]. A number of powerful tools for exploring libraries for cheminformatics and related applications are becoming available [60].

EXAMPLES OF AI IN BIOPHARMACEUTICAL DISCOVERY

The activity of immunogens, receptor traps, and enzymes are often mediated by a small number of functional residues, with their domains properly presented by the overall protein structure. We have seen how AI-empowered AlphaFold can predict protein structures from amino acid sequences. This success created hope that such neural networks, trained on well-characterized protein sequences and structures, could also help create novel proteins with understood functionality.

GPT4

Open AI's GPT4 is a type of generative AI primarily designed for natural language processing. Such applications are now demonstrating capability in the design of therapeutically functional proteins from simple molecular specifications. This innovative approach, known as protein language model transfer, involves adapting the underlying algorithms to interpret and generate protein sequences based on simplified molecular descriptions. The model is trained on datasets containing information about known protein sequences and their associated functions.

BioGPT

The success of GPT4 inspired the development of bio-specific models such as BioGPT, a pre-trained language model that provides text mining and generation for biomedical domain research [61]. For example, we are seeing the design of novel protein structures containing prespecified functional sites in an effective orientation customized for a particular use or disease therapy [62].

With this training, BioGPT can generate new protein sequences based on provided molecular specifications. These generated sequences undergo evaluation using computational models and simulations to assess their potential for therapeutically functional

It is valuable to realize that AI supports new, previously impossible, capabilities and can radically speed up existing data processing activities and applications.

properties. Nevertheless, experimental validation in the laboratory remains a critical step in verifying the actual functionality and safety of designed proteins.

Chimeric Antigen Receptor T cell Technology

ML techniques enabled researchers at University of California, San Francisco—in collaboration with a team at IBM Research—to expand chimeric antigen receptor T cell (CAR T) technology and make design activities more quantitative and predictive of functionality. First, they constructed a library of CAR Ts containing synthetic costimulatory domains, built from combinations of signaling motifs. Then, using neural networks, they discovered key design rules of the system, which they describe as the ability to "decode the combinatorial grammar of CAR signaling motifs," [63]. This work illustrates how ML tools employing libraries of domains support the engineering of receptors with desired phenotypes [63].

ProSurfScan

ProSurfScan is a new commercially available program to model the compatibility and binding mode of a candidate on different regions of a protein surface [64]. There, the protein surface is represented as a graph of nodes defining local supramolecular interaction features. Convolutional neural networks can then agnostically estimate candidate interactions with distinct regions on the protein surface.

Integrated Biosciences

Researchers at the University of California, Santa Barbara are collaborating with Integrated Biosciences, a biotech combining synthetic biology and ML to target aging. Maxwell Wilson, co-founder of Integrated Biosciences and assistant professor at University of California, Santa Barbara. explains, "Our synthetic biology platform enables previously impossible drug discovery because it avoids inducing the collateral damage caused by chemical poisons, enabling us to observe direct effects of drug candidates on the cell's stress response and perform fast and accurate target deconvolution" [65].

EMERGING THERAPEUTIC MODALITIES AND TECHNOLOGIES

We are seeing remarkable developments in advanced therapy medicinal products (ATMPs) therapeutic entities, the means to deliver them, and the technologies employed in their production. AI is becoming essential in handling the amount and type of data coming from the many high-throughput and high-density analytics and screenings employed here [66]. Deep learning algorithms such as recurrent neural networks are well-suited for analyzing massive amounts of multivariate time-series data. These algorithms assist in tracking changes over time from assays of cell type-specific responses. This includes the expression of specific genes from cultured cells and biobank submissions.

AI's deep learning supports a high-level analysis of cell motion, microfluidics, and panomics. New single-cell analysis techniques allow the study of an individual cell's behavior in tissue and omic contexts. This leads to a deeper understanding of cellular heterogeneity and disease mechanisms. There, AI is providing a deep point-to-point analysis of hundreds of individual cells. Such an extension of single-cell multiomics is yielding more insightful systems understanding than the results of the averages of millions of cells. Recently, improvements in single cell–whole genome sequencing are showing promise in tumors that display a mosaic of genetic variation, or subclonal mutations that make the tumor more aggressive [67]. One can only imagine the understanding to be revealed as AI classifiers are applied to this data.

There are many other AI-powered applications aiding in therapeutic candidate and DT understanding, such as virtual reality and augmented reality. These are allowing us to visualize and even interact with complex biological structures and datasets. Such capability was reviewed in a Computer Vision and Pattern Recognition Conference June 2024 in Settle [68].

Finally, it is valuable to realize that AI supports new, previously impossible, capabilities and can radically speed up existing data processing activities and applications. For example, AI-driven natural language processing does not really change the nature of literature review, but it dramatically reduces the time involved in examining and summarizing vast amounts of research and medical literature.

EMPLOYING EVIDENCE-BASED ASSOCIATIONS

By examining the structural, biological, or functional similarity of putative DT in diseases of related ontology, a new initiative, The Disease Ontology, promises an open-source tool for the integration of biomedical data associated with human disease features and mechanisms. It hopes to serve as a reference framework for multiscale biomedical data integration and analysis that will help strengthen the disease information ecosystem [69]. In linking disparate datasets through disease concepts, it promises to provide a computable structure of inheritable, environmental, and infectious origins of human disease.

AI can efficiently enable comprehensive multiparametric collection, development, and analysis of the enormous sets of emerging research data with the vast body of biomedical literature,

clinical trial data, electronic health records, and other sources. This aids in identifying potential DT in specific patient populations and even personalized medicines. By searching through various real-world patient data, including published off-label use, pointing out the many primary and off-target clinical effects of a drug, AI can help predict candidates in the context of complex endocrine, immune, or metabolic pathways. ML modeling of the multiplex interaction networks of existing therapeutic entity activity with novel candidate DT and disease modulators aids in better understanding the relationships between them.

CHALLENGES

The lack of transparency ("black boxes") in some AI algorithms makes it more difficult to know whether a system is fair, accurate, and complete. An AI system can also be inappropriate based on flawed data sets or assumptions about its application context, user understandings, or user requirements and procedures. Explainability and transparency in algorithms and their updates is desired to ensure accuracy and compliance in outputs, yet they remain difficult to achieve. Collaboration between domain experts, data scientists, and regulators is crucial to establish and maintain the quality, reliability, safety, and alignment of AI systems throughout the entire product life cycle [70].

Regulatory and Validation Requirements

Regulatory requirements for DT discovery are much less stringent than those for clinical trials or drug approval. They are limited to, for example, International Council for Harmonization (ICH) and good laboratory practice guidelines on data integrity and transparency as well as potential public funding requirements for specific reporting and data sharing mandates.

However, the increasing size and complexity of systems are making it more challenging to identify critical functionalities, define appropriate testing, and establish acceptance criteria that meet sponsor internal guidelines for software reliability, robustness, and performance efficiency. Software-as-a-Service (SaaS), risk-based validation, computer software assurance, and Pharma 4.0™ initiatives determined a significant change in validation demands and solutions. And the unique aspects of AI now further this need for development in validation approaches.

Cybersecurity and Internal AI Processes

The growing concern of cybersecurity refers to technologies and policies to protect data, computer systems, and applications against potential threats such as unauthorized data or systems access and attacks. There are actually two categories of security topics associated with AI.

Secure AI refers to the steps taken to ensure the implemented AI systems are secure from such cyberthreat approaches as brute force, denial of service, and information harvesting. It's about designing AI systems that are protected from unauthorized access or alteration. Both model integrity and data security are topics of secure AI.

On the other hand, AI cybersecurity refers to AI techniques as a tool to detect, prevent, and respond to cyber threats by enabling improved network security, anti-malware, and fraud detection. There, AI tools are used to identify intrusions by either analyzing communications in real-time to detect and respond to threats, or by analyzing historical data to predict system vulnerabilities and avenues of potential attack. Although it's true that the internal processes of some, even static, AI algorithms can be hard to interpret, this is not a universal characteristic. An emerging standard in the field of AI called the Open Neural Network Exchange (ONNX) is working to address this concern. ONNX aims to create an open ecosystem where AI models can be developed, trained, and deployed across various frameworks and tools, provided by many organizations promoting transparency and interoperability.

Interoperability

Vertical interoperability in the pharmaceutical sector underscores the critical requirement for a standardized repository of algorithmic tools and foundational structures. These are essential for creating and deploying AI-driven applications and methodologies across a diverse range of proposed concepts and use cases within the pharmaceutical realm.

Horizontal interoperability, on the other hand, centers on the demand for high-quality data sourced from a variety of equipment, hardware, networks, and software utilized throughout a drug's life cycle. AI-based models are particularly sensitive to insufficient, biased, or incomplete data sets. To mitigate this challenge, it is necessary to establish improved standards for data governance, curation, and exchange. Data integrity in drug manufacturing, as outlined in the *ISPE GAMP® 5 (Second Edition)* guidelines, emphasizes maintaining the accuracy, completeness, and consistency of data throughout its life cycle, ensuring the reliability and compliance of pharmaceutical processes [71].

Transparency

Applications associated with ONNX enable model portability, allowing the same model to be used in different environments. This enhances transparency and also encourages collaboration and sharing of best practices in AI model development. Therefore, the adoption of standards like ONNX is a significant step toward making AI systems more transparent, accountable, and understandable. Advancements in AI technology, coupled with standardized practices, are steadily reducing the opacity associated with some algorithms [72]. Further, the interdisciplinary nature of effective implementation necessitates seamless collaboration between data scientists, domain experts, and regulatory professionals to ensure a harmonious integration of these technologies into drug manufacturing processes.

Drug Development

Lastly, there have been published concerns regarding the use of AI in drug development, including considerations of the failure of some clinical trials following AI-supported candidate identification.

Although this is obviously concerning, it should be noted that these events are not outside the current statistics of trial success, and that the particular causes for the trial failure have not yet been established. Furthermore, it is implicit that candidate targets, as well as early "hits" or lead candidates, can be examined and verified using any classical means available.

CONCLUSION

AI has demonstrated significant power in medical research, diagnosis, and therapy commercialization. It aids in explaining biological phenomena through a structured and comprehensive assimilation, analysis, and interpretation of biological big data. This provides researchers and clinicians extraordinary computational capacity in such comprehensive pursuits as those involving panomics. The value of such DT identification is being driven by innovations in both discovery technologies and in such novel therapeutic modes as precision oncology.

AI is empowering the methodologies, applications, and emergent frontiers that underlie drug discovery and delivery throughout the entire drug life cycle [73]. The accelerated application of AI in DT identification profoundly enhances our understanding of effective therapeutic interactions, and it expedites the entire process from target discovery to drug manufacturing [74]. This accelerated AI-driven approach holds immense value for patients by streamlining the development of more targeted therapies. Ultimately, this will lead to more efficient and personalized treatments with the potential to reduce off-target effects and improve clinical outcomes.

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REEVALUATING TRANSFER OF RTU Containers into Grade A

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At first glance, ready-to-use (RTU) primary packaging material (tub systems) give production lines more flexibility and reduce container preparation complexity for aseptic fill/finish operations. However, the aseptic introduction of RTU tub systems requires a thoroughly designed transfer process to avoid contamination of the sterile RTU items and the aseptic core.

With more industry experience in technical transfer solutions and the release of the European Commission's updated good manufacturing practice (GMP) guidelines, specifically Annex 1, the section on the manufacture of sterile medicinal products [1], it's time to reevaluate transfer setups using a holistic quality risk management approach.

INTRODUCTION

"The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination," per the EU guidelines [1]. RTU tub systems can serve as an alternative. They are commonly presented in nests or trays to avoid glass-to-glass contact. Depending on the type of pack style (i.e., syringe, vial, and cartridge), the containers are pre-assembled and pre-treated (i.e., washed and siliconized). RTU packaging material for aseptic processing comes pre-sterilized in their overpack, either by irradiation (gamma or beta irradiation, limited to plastic packaging material) or ethylene oxide gas treatment.

Besides adequate sterilization, the main challenge to using RTU is getting the sealed containers recontamination-free into the grade A core of the isolator or restricted access barrier system (RABS) for filling/finishing.

Two different approaches have been successfully established in the industry:

- No-touch transfer (NTT): Stepwise unwrapping/debagging in higher-quality cleanroom grades, either automatic or semi-automatic debagging; and for NTT, single and double-bagged tubs are established in the market.
- Debagging the closed tub and following re-disinfection of the tub by one of the following techniques:
  - Electron beam irradiation
  - Chemical disinfection (commonly by hydrogen peroxide (H_2O_2) fog/vapor
  - Pulsed white light with ultraviolet (UV)

These techniques can achieve safe transfers (there are references to approved production lines within the industry).

REGULATORY FRAMEWORK

Annex 1 and other guidelines do not specifically address transfer of RTU tub systems into grade A [1]. However, statements of these guides also apply for RTU transfer or can be interpreted as being applicable. Here are some popular citations:

The FDA's 2004 Guidance for Industry [2] establishes transfers into the aseptic zone as a critical process: "It is critical to adequately control material (e.g., in-process supplies, equipment, utensils) as it transfers from lesser to higher classified clean areas to prevent the influx of contaminants." However, this guidance focuses more on the number of transfers and the rapid transfer port technology. When this guidance was published in 2004, nested RTU pack styles were relatively new in the market and not yet widely used.

The description of a nest transfer from an article on the history of prefilled syringes in 2015 [3] says: "Ready-to-use syringes are nested in tubs that are sealed and surrounded by at least two polymeric bags. The bags surrounding the tubs of syringes are removed progressively as the tubs are transferred to the more controlled areas of the manufacturing suites. The first bag may be

removed in the grade C (ISO 7) area and then placed in a transition zone where the second bag is removed before transferring the sealed tub into the grade B (ISO 5) area. Finally, an operator will place the sealed tub in the grade A (ISO 5) area and the Tyvek seal will be removed either manually or by the equipment automatically."

The process described was manual because automatic and robust bag removal systems were rare and double bags couldn't be peeled automatically at all, so the first removal had to be done manually. This situation created the need for safer transfers with basically no manual intervention. Sections of Annex 1, with relevance for the transfer of RTU pack styles should be considered [1]:

Section 4.10

This section gives a general heads-up to the process risk of any transfer in and out of grade A environments. This applies to all kinds of goods to be transferred regardless of their transport packaging. This includes equipment such as tools and tweezers, components such as stoppers, and pre-sterilized pack styles of vials and syringes.

Section 4.11

This section states that any transfer be performed in a unidirectional process, ideally with a direct interface between a sterilizer and grade A ("double door autoclave or depyrogenation oven/tunnel") [1]. This is not possible for RTU because RTU material rarely gets autoclaved. Ethylene oxide or gamma irradiation are the sterilization processes of choice for RTU with gamma for plastic containers only.

These processes must be performed off-site in dedicated facilities. RTU material is then transported in multiple shells (i.e., tub, inner bag, outer bag, liner, or carton) to the manufacturing site. Once there, it must undergo a safe transfer procedure for introduction into grade A fill/finish.

Section 4.12

This section asks for protection of materials transiting through grade B ("Equipment and materials (intended for use in grade A area) should be protected when transiting through grade B area") [1]. This protection is provided for RTU pack styles, which come in (multiple) wraps to the aseptic manufacturing line. The concept of this section is based on a core aseptic processing cell in grade A quality, which is surrounded, or at least supplemented with a grade B infeed. The ideal "onion skin" concept features a transfer from grade D (or clean nonclassified area [CNC]) to a grade C classified area [1]. From there, the material should pass through grade B ("transit") and be introduced to grade A [1].

This concept can be varied with additional measures. Annex 1 states that the minimum required cleanroom grade for an open isolator environment is grade C (Section 4.20, among others) [1]. The transfers into and out of an isolator do not pass a grade B. This, however, is fine as long as differential pressure and unidirectional airflow (UDAF) of grade A air provide a barrier against recontamination. The transferred goods must be sterile.

Section 4.18

This section covers barrier technologies like isolators and RABS: "The hazards introduced from entry or removal of items during processing should be minimized and supported by high capability transfer technologies or validated systems that robustly prevent contamination and are appropriate for the respective technology [1]." However, it remains unclear what features and controls are expected to make a specific technology highly capable for transfer. The Barrier Technologies chapter does not include more details for transfer" [1]. However, the chapter "Aseptic Preparation and Processing" in Section 8.10, Table 4, guides typical examples of operation in different cleanroom grades [1].

The description of operation examples in grade A "Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials" does not describe the typical situation for introducing packed/wrapped RTU containers [1]. This is covered more under grade B examples: "Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A [1]."

The examples list is incomplete and does not give guidance specifically for RTU pack style transfers. It reflects more a static exposure of a protected item before a transfer process ("conveying or staging") and not necessarily the transfer situation itself [1].

Section 8.46

This section is part of the sterilization chapter and addresses the RTU situation from the sterility point of view: How to maintain sterility during storage and transfer [1]. Multiple sterile coverings are listed and a stepwise removal during transfer into grade A is described: "…configuration of the sterile pack allows the items to be readily disinfected during transfer by operators into grade A (e.g., by use of multiple sterile coverings that can be removed at each transfer from lower to higher grade) [1]." Section 8.46 describes the typical NTT situation with multiple covers.

Section 8.47

This section gets more specific on the transfer technique and gives advice on re-disinfection: "…this should be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging [1]." The concept behind this is that the bioburden on the outer covering of a sealed and pre-sterilized package will be removed by disinfection during the transfer step. This is an obvious requirement for keeping grade A free of microbiological contaminants. However, it does not necessarily apply to the RTU situation with multiple coverings (this is covered in Section 8.46).

The validation requirements on the packaging of the pre-sterilized RTU tub systems is addressed in Section 8.48 stating that the RTU user validate the full supply chain process, from sealing and sterilizing at the RTU supplier to transfer into grade A. Besides thorough validation, Section 8.48 also demands a check prior to use: "…the integrity of the sterile protective barrier system for each of

Continuous learning from production data and quality assessments in a defined risk review process helps keep risk management updated.

the sterilized items should be checked prior to use [1]." In case of RTU kits, this check is commonly performed visually.

Both approaches (NTT and re-disinfection) are valid and could be linked to Annex 1 without being directly addressed by it (creating uncertainty and misleading interpretations). Consequently, this paper examines the details of RTU transfer solutions from the perspective of quality risk management, demonstrating that there exists a multitude of technologies for safe transfers.

QUALITY RISK-BASED APPROACH

The availability of high-quality medicines is a key intention of Annex 1. In the dualism of quality and availability of medicines, a balance of measures must be taken to the benefit of patients. The tool set for this is a holistic quality risk management process according to ICH Q9 (R1) [4]. It starts with a risk assessment, which consists of hazard identification, risk analysis, and risk evaluation. After risk assessment, the process adds appropriate and effective risk control measures.

The third element of risk management includes risk communication, which helps to install an orchestrated mitigation process and keeps team members informed. Continuous learning from production data and quality assessments in a defined risk review process helps keep risk management updated. This is documented and kept up to date in the contamination control strategy (CCS), according to Annex 1 [1].

RISK ASSESSMENT

The primary risk during RTU transfer is product contamination by germs, originating from any point in the supply chain. Contamination could occur at the RTU manufacturing stage (despite validation and controls), during transportation to the fill/finish facility, during warehousing or unpacking, or within the transfer section itself, potentially leading to adverse patient reactions.

In the first approximation any kind of contamination (viable or nonviable particulate), the contamination is taken as a hazard, which should be addressed. Risks associated with the hazard could come from the following:

- Contaminated surfaces in the transfer section and unbagging equipment
- Operator interventions (with open doors or through glove ports)
- Insufficient separation of the processing area from the operator's environment (through barrier or damaged HEPA filters)
- Contamination carried into the product flow during the material feed of the debagging station

The probability of potential risks depends very much on the configuration of the equipment and handling practice of the operators, which must be addressed in a thorough process design. In a robustly automated debagging and transfer process, risks deriving from operator interaction are limited to routine handling of package material (material feed at debagging station or, in case of double-bag transfer, at the first debagging station) and manual handling of environmental monitoring goods through glove ports.

Risks coming from unplanned operator interventions (e.g., with open-door access of the transfer section barrier to fix a given problem) are very critical. These risks increase the likelihood of recontamination of the inner bag and, in consequence, recontamination of the tub. This also impacts the risk severity, as particulate might be transferred from the operator. NTT should be "no touch" to avoid indirect contamination routes.

The risk analysis should also cover the second debagging step and the situation with the inner bag open and tub transfer into the grade A aseptic core zone. Even if recontamination of the inner bag should have happened (via whatever contamination route), contamination spreading to the sealed tub and transferring into the grade A zone should be avoided.

RISK MITIGATION MEASURES

The first measure to reduce recontamination risks is to apply a cleanroom approach in the transfer section, comprising a barrier enclosure, a pressure concept with higher pressure level within the transfer section (compared to the environment), HEPA filtration of incoming air, and UDAF. This is combined with a pre-cleaning and pre-disinfection step before production starts.

Additional measures needed for operating a grade B or grade A environment include the control of the cleanroom quality by sensors (e.g., differential pressure levels upstream and downstream terminal air filters), particle counting, active viable sampling, and settle plates. Whatever grade is claimed for transfer arrangement is a result of a thorough risk analysis and must be reflected in the CCS with an appropriate process design, including technical and operational measures. The same applies to the inactivation efficiency when a re-disinfection process step is part of the transfer.

RE-DISINFECTION

Electron Beam Treatment

The first representatives of re-decontamination systems were electron beam systems (see Figure 1), which provide electron irradiation to re-disinfect the surface of the tub [5–6]. The irradiation dose of at least 15 kilo-Gray (kGy) is a validated industrial standard to inactivate six logs of any kind of microorganism on the outside of the tub and at locations just below the Tyvek cover sheet [7].

There are many established systems that provide a 25 kGy dose (equivalent to a 12-logs reduction of bacillus pumilus spores). These bring a higher assurance level but increase exposure of RTU containers to oxidative side products of the process.

The inactivation dose must be achieved under the nonwoven cover because the cover is not flush in shape with the sealed area (overhang), and therefore the gripping tab corner could potentially, but very unlikely, be contaminated. Due to this penetration of the nonwoven lid, electron beams could hit the glass containers and result in discoloration. Therefore, RTU manufacturers deliver specific electron beam packs with an extra (double) sheet of Tyvek inlay in the tub to decrease the dose at the surface of the glass containers (see Figure 2) [8]. Tubs for electron beam re-decontamination are commonly wrapped in a single (outer) bag because potentially transferred contamination during bag opening would be inactivated anyway.

Side Effects

A side effect of electron beam irradiation at atmospheric pressure is the generation of nitrogen oxides and ozone in the irradiation zone, which must be exhausted quantitatively. Residual concentrations of these gases are harmful to operators and products. Because the glass containers are protected by the double Tyvek liner, there is no dose at the container level; therefore, suppliers can also demonstrate no ozone at container level. Electron irradiation also generates some X-ray emissions, which must be blocked by geometrical measures (a labyrinth-like arrangement of the parts flow in the electron beam tunnel) and armor plating of the tunnel with lead sandwich composites.

Electron Beam Design

Well-designed electron beam tunnels have grade A in the transient zone between electron beam curtain (re-decontamination) and isolator infeed. This requires UDAF airflow and pre-disinfection, commonly performed with an H_2O_2 bio-decontamination process before production starts. Additionally, a pressure difference between isolator (e.g., + 25 pascals [Pa] to grade C isolator environment) and re-decontamination zone (e.g., – 20 Pa to grade C electron beam environment) generates a strong counterflow of grade A air. This flushes the re-decontaminated tub on its way to the isolator. Generally, the transient zone is particle controlled using HEPA filters and, as an option, they can be equipped with particle counters. Viable monitoring depends on electron beam type: the accessibility to exchange nutrient media might be limited. Well-designed systems offer remote viable sampling points.

Electron beams need lead shielding to protect operators from X-ray exposition. This results in a significant weight of the systems, which must be considered for the facility design (maximum load on the floor per square meter). However, commonly the electron beam systems are very compact and space saving in design. Validation of an electron beam process is straightforward: color strip dosimetry is commonly applied to determine the dose distribution on the tub surfaces.

Figure 1: Electron beam for re-decontamination of tub outside.

Photo Credit: SKAN AG

Figure 2: Picture from typical RTU tub and bag kit. The liner right above the syringes could be thicker (or double) for use with electron beam.

Photo Credit: Gerresheimer AG

Alternative technologies were explored to address the recontamination risk by tub transport, storage, and handling of an already sterile (ex-works) tub. Chemical re-disinfection or an alternative physical disinfection process, such as UV or pulsed white light with UV shares of spectrum, was investigated as alternatives to electron beam and NTT.

PULSED LIGHT

UV is a clean and simple technology with a simple dose control capability. It treats the outside only (no dose absorption inside the tub) and creates little or no relevant oxidative atmosphere in the treatment chamber. This could deteriorate materials or

generate persistent residues that might harm the product [9–10]. With the pulsed light approach, flashes (e.g., 300 milliseconds) transfer enough energy for many types of microorganisms to cause cell layers to burst and initiate DNA decomposition. But some pigmented germs (like aspergillus brasiliensis) might be persistent.

The disadvantage of UV is the low penetration capability. Nontransparent layers shield germs from interaction with UV irradiation. For example, the nonwoven cover sheet cannot be penetrated and so the gripping tab corner of the tub will not be treated. Multilayer stacks of microbiological contaminants will also not be completely inactivated, as the residues on the top layers might shield the bottom layers from UV energy (i.e., shadow effect).

CHEMICAL AGENTS

A chemical bio-decontamination agent must get into contact with all tub surfaces. The contact time must be short to achieve a high output (e.g., six tubs per minute) and residuals of the disinfection reagent must be aerated within the shortest time to avoid contamination or deterioration of the product.

A common chemical for re-disinfection is vapor-phase hydrogen peroxide (VPHP)[11]. The vapor has the capability to penetrate the nonwoven cover sheet and thereby provides decontamination of the gripping tab corner. However, hydrogen peroxide will also migrate into the tub and interact with the packaging material. For glass-only containers, this is not an issue because hydrogen peroxide will be aerated/diluted as soon as the tub is opened and exposed to UDAF within a short time. With rubber and polymer components (e.g., tip caps), however, this might take much more time. For oxidation-sensitive products like proteins, a risk analysis backed by data must show that peroxide residuals stay below a concentration level which might harm the product quality.

Vaporized hydrogen peroxide is the decontamination chemical applied to RTU tubs in a recently introduced continuous transfer system vapor-phase hydrogen peroxide [12]. In this setup, the contact with the hydrogen peroxide vapor is only seconds long. Therefore, a high vapor concentration (6.000–8.000 parts per million [ppm]) is provided to the outer surfaces of the tub. Up to six tubs per minute are claimed as maximum decontamination and transfer speed. The tubs must be unbagged before introduction into the bio-decontamination tunnel. This could be done with an automatic or semi-automatic debagging machine.

The bio-decontaminated tubs are aerated by HEPA-filtered UDAF with their nonwoven lid still sealed. The second step of aeration happens as soon as the lid is peeled off in the fill/finish isolator with grade A airflow (UDAF). Compared with the low-output setup, this system has the same advantages and disadvantages: effective disinfection of the tub surfaces (6 log, also in the gripper tab area), but penetration into the tub, which leads to residuals that must be removed before filling oxidation-sensitive products. As the tubs are moved in the tunnel during the bio-decontamination process, it is not possible for any part of the tubs to avoid contact with the chemical disinfectant.

RISK CONTROL: NTT

NTT concepts rely on a robust process design, which starts with safeguarding the sterility of the bag inside, preventing recontamination during unwrapping/transfer, and removing particles before the tub enters the tub opening and filling section. Because there is no re-disinfection step involved, each step must be well controlled and should be automated for reproducibility and separation from operator.

In the case of double-bag systems, the concept for folding the inner bag varies with packaging material vendor. An automatic unfolding/opening process must be able to flexibly handle whatever tub/bag configuration comes on the line. However, this flexibility might result in rare handling errors, which could be addressed with an intervention for keeping the product flow running [13].

Intervention could principally mean robotic intervention (no need for operator access), manual intervention through glove ports (doors stay closed), or manual open-door intervention. This last option should be avoided wherever possible. Depending on the type and frequency of interventions, different cleanroom requirements and routines are needed.

Avoiding jams by robust debagging technology is a major driver for risk reduction. This includes sourcing the highest quality packaging material with a reproducible folding of the inner bag. In case of stops created during the unfolding step, transport or debagging, the next line of defense is to prevent particulates from being transferred during the following intervention from the operator or the operator's environment to the process.

For NTT, an open-door intervention is clearly the riskiest measure to fix a problem. But depending on the problem and the ergonomic situation, it could also be the last resort to resume production. Interventions through glove ports are significantly reducing the risk, particularly when performed with sterilized tools.

After intervention, the cleanroom (and surface) quality of the transfer section must be recovered to validated levels. This might include sporicidal treatment and dwell time on all surfaces in and close to the intervention area. Packaging material, which has had contact with gloves or tools during intervention, needs to be removed and should not be further processed.

Following the path of potential contamination, "blockage – open door intervention – transfer of contaminant," the last line of defense is the airflow design at the debagging and transfer station. As long as the inner bag is closed, the residual risk of contamination transfer to the tub and via the tub into the grade A zone is very low/negligible. In the moment the bag is opened with a knife, the tub should not have any contact with the inner bag around the open bag "mouth." This is also important for the following pushover of the tub into the aseptic core zone.

DOUBLE-BAG SYSTEMS

A basic requirement for NTT is a robust bag opening and tub transfer system. Double-bagged RTU packages are becoming

Figure 3: Vacuum chamber (labeled #32) for unfolding the inner bag [14].

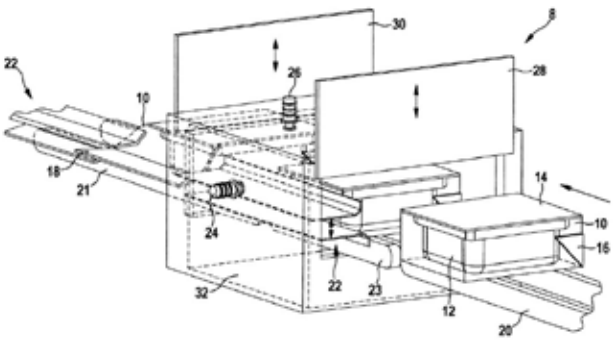


Figure 4: Retraction (labeled #68) mechanism [15].

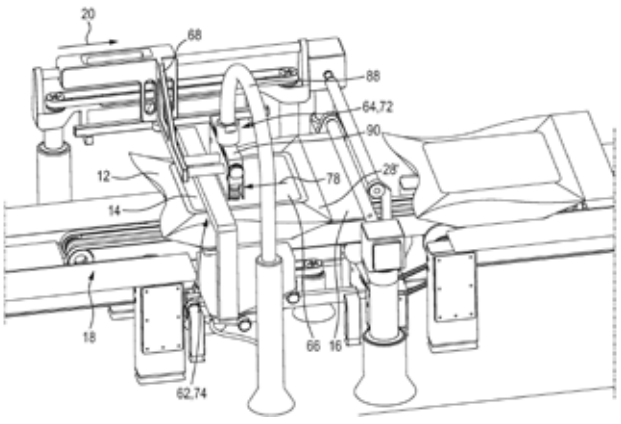


Figure 5: Spiking mechanism (labeled #40) [16].

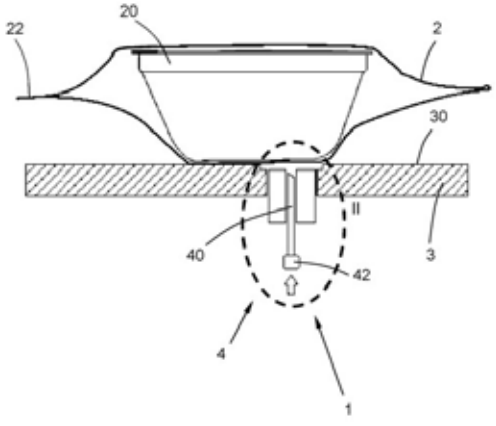
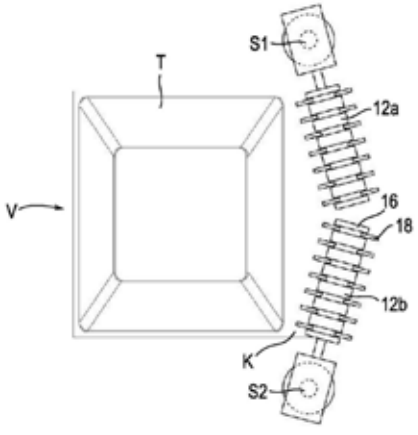


Figure 6: Bristle rollers (labeled #12a and #12b) [17].



more popular due to double safety against damage and support of a stepwise transfer into higher-grade cleanroom environments. In the past, bag opening of double bags was commonly a manual process because the inner bag is folded around the tub and must be expanded before an automatic opening process of the inner bag can be started. Otherwise, the knife would not completely open the bag and, consequently, the tub could not be transferred without additional manual cutting intervention.

Meanwhile, different automatic technologies in the market are available to expand the bag without manual steps, which reflects Section 2.1.i. of Annex 1: "…the use of appropriate technologies… should be considered to increase the protection of the product from extraneous sources of endotoxin/pyrogen, particulate and microbial contamination… [1]." Some technical solutions are listed next.

Vacuum Chamber

The vacuum process starts with the transfer of the tub into a vacuum chamber. Doors are closed and pressure is lowered, causing the bag to expand due to the pressure difference between the inner bag and the chamber. After aeration of the chamber, the bag presents an easy-to-cut flap on the side of the tub. After releasing the tub from the vacuum chamber (double door load lock style), it can be transferred to the bag cut and removal machine (see Figure 3) [14].

Grab and Retract

In an alternative process, the tub with the inner bag is presented to roller arrangement, which grabs the plastic film and unfolds the flap by a movement against the transport direction. The package is retracted, which stretches the flap to be cut. From there, the tub with bag can be transferred to the cutting and bag removal station (see Figure 4) [15].

Pressurization by Spiking

The application of a pressure difference between the inside of the inner bag and the environment is the basic principle of another solution for unfolding and grabbing the flap for the bag opening process. In this concept, a puncture with a hypodermic pressurized needle into a piece of plastic film of the inner bag, which is grabbed by a suction dome principle, creates an overpressure in relation to the environment. This helps inflate the bag and allows the flap to be unfolded and cut. This process can be combined with a vacuum dome to increase the pressure difference (see Figure 5) [16].

Grab with Bristles

Instead of inflating the inner bag, this solution uses the friction between the plastic film and a set of rollers with bristles to grab the folded flap of the inner bag. The two rollers are positioned one above the other and rotate against each other to pull the flap between them [17] for stretching and cutting (see Figure 6).

Tub Opening and Filling in RABS

A very common expectation is to do transfers from CNC to D, to C, to B, to A (or vice versa). In the case of a RABS line, the aseptic core (grade A) has a grade B environment. For unplanned interventions and routine manual operations (e.g., change of settle plates or opening of rapid transfer ports), gloves are required. In exceptional cases, the doors might be opened, but this is a very critical process and it must be based on a detailed description in the CCS and properly documented. Partial line clearance together with re-disinfection of the area of intervention might be an appropriate measure to get back into production. As with other equipment design, the door opening is combined with the end of batch.

NTT WITH DOUBLE-BAGGED RTU PACKS

Although NTT with double-bagged RTU packs in RABS lines is not common, it should still be noted. There are two different cleanroom settings possible for transfer into RABS lines with NTT and double-bagged RTU material. These are a grade B inside transfer section and a grade C inside transfer section.

Grade B Inside Transfer Section

The first bag is removed in a grade C environment and transferred into a grade B environment with the inner bag still closed to prepare for the opening of the inner bag and transfer into the fill/finish core. The transfer section between the bag opening units needs to have glove ports for handling goods, which are needed to perform environmental monitoring (EM) (e.g., plates for active and passive viable monitoring). This is a requirement for claiming grade B.

The same glove ports could be used to fix problems with tub transfer and bag opening processes. The environment of the transfer section could have a grade C classification. In traditional aseptic manufacturing, this would require a pressure difference between the operator environment and the inside of the transfer section of at least 10 Pa, according to paragraph 4.14 of Annex 1.

To achieve this pressure difference, the setup would need a closed RABS-like design. Alternatively, the operator environment is a grade B (same as inside). But this arrangement (grade B in a grade B environment) is rare. It might make interventions easier because under the regime of standard operating procedures (SOPs) doors could be opened to fix jams. Nevertheless, for interventions and exchange of settle plates or active air sampling, gloves would still be preferable.

Because no openly exposed product or unprotected components are handled in the transfer section, a grade B could be achieved (i.e., classification, monitoring) without claiming pressure difference of at least 10 Pa, according to paragraph 4.14 of Annex 1. Airflow visualization should support the separation claim.

Grade C Inside Transfer Section

Because the tub is still sealed and containers are not exposed to the environment, the inside of the transfer section could principally also be classified as a grade C cleanroom with ISO 5 airflow. With the opening of the inner bag, the tub will be flushed with grade A air from the isolator (pressure difference) and filtered ISO 5 airflow from UDAF of the transfer section, as described previously. The risk of recontamination by a lower-grade process environment depends on the process. This is especially true on the airflow design in the opening step of the inner bag before the tub enters the grade A zone of the aseptic core.

The operator environment would be a grade C in this configuration. That is, interventions could be performed via glove ports or under strict adherence to detailed SOPs by door opening. Direct touch of the inner bag should be avoided as sterilized tools would be preferable. The particle status can be monitored to control grade C, but clear separation between the inside of the transfer section and the operator environment is not shown in data (both grade C). It boils down to a holistic risk evaluation of packaging material and transfer and to operator handling to make this simple setup robust.

The doors should stay closed all the time. If there is a need for opening the doors to fix a jam, material disposal, a disinfection program, and further safeguards should be applied to avoid any cross contamination during interventions. These safeguards could include sterile gloves for operators and optionally UDAF above door swings. Airflow visualization studies should support the separation claim.

OPEN ISOLATOR TUB OPENING AND FILLING

Grade A Inside Transfer Section

The transfer of the tub and opening of the inner bag is handled in an isolator section upstream to the tub opening isolator with an operator environment of grade C. Although there is no installation known to the authors, this is principally possible, but requires a significant additional effort compared with an open RABS. It would be the most secure situation but would come with some technical and handling challenges such as the disposal of the inner bag in a contained setup, e.g., with a rapid transfer waste port.

Also, in this configuration, a pressure difference between the tub opening and the section for opening or removal of the inner bag would make sense to avoid particulate from the bag opening being transferred into the open tub. Therefore, a pressure cascade from the isolator section to the opening section would have to be defined and monitored.

Interventions in the transfer section to correct the position of the tub or assisted unfolding of a sticky/flappy inner bag must be performed through glove ports. Opening the door would result in a major interruption with repetition of the bio-decontamination

Figure 7: Typical NTT arrangements for RTU transfer systems in front of an open isolator: A) NTT with double-bag opening and B) with electron beam. Renderings are not scaled.

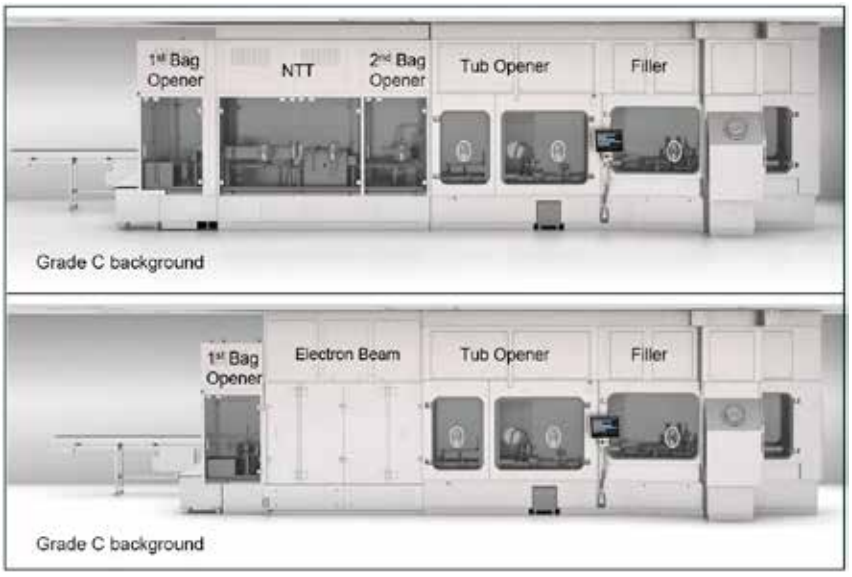


Photo Credit: Syntegon Technology GmbH

cycle and additional challenges in the mousehole area. Overlapping bio-decontamination of the seals would hardly be possible.

Grade B Inside Transfer Section

As described previously in the RABS section, the first bag is removed in a grade C environment and transferred with the inner bag still closed into a grade B environment to prepare the bag for opening. Grade B requires cleanroom monitoring (e.g., particle counter, active air sampler, settle plates, and monitoring of filter pressure difference). For the exchange of EM media, gloves need to be installed in a RABS-like barrier. The gloves can also be used for manual interventions so that doors can stay closed.

A classified grade B in a grade C environment would require a pressure step between the operator environment and the inside of the transfer section. This could only be achieved by a closed RABS with return air ducts. But the operator environment could principally be either a grade B or a grade C. Grade B would be exotic. This is because in a fill suite layout with an open isolator there is no other grade B area that could be expanded.

Placing the grade B transfer section in a grade C environment without pressure difference from grade C to grade B is combined with a pressure step from the transfer section to the isolator inside (grade A). This results in the overflow of grade A air into the bag opening area and forms an "grade A air jacket" around the tub. The required pressure difference is therefore only moved from grade C/B to grade B/A and combined with automated stepwise removal of covers, as described in section 8.46 of Annex 1 [1].

Grade C Inside Transfer Section

This convenient approach uses the isolator in a grade C (operator) environment, which is expanded by the area of the transfer section. Integrating gloves into the doors might address risks from direct operator intervention. The bags are still closed, and tubs are still sealed. Interventions in the opening and unloading process of the inner bag should be prohibited anyway. A major issue in this area would lead to the end of batch. Two examples of typical arrangements for RTU tub transfer into an open isolator are shown in Figure 7. One example is with NTT and one is with re-decontamination represented by an electron beam setup.

Closed Isolator Tub Opening and Filling

As per the definition in the Annex 1 glossary [1], closed isolators do not have a continuous flow of material into and out of the enclosure. In this case, tubs must be transferred and opened internally before fill/finish processes can start. A common approach involves an H_2O_2 chamber with a mousehole to fill/finish section of the work cell. The tubs must be unbagged manually and loaded into the hydrogen peroxide treatment chamber still sealed with the nonwoven cover. The hydrogen peroxide vapor penetrates the tubs and bio-decontaminates the tub outside with some residual concentration inside.

The chamber for this does not have a defined classification but provides HEPA-filtered air to flush the compartment. After the bio-decontamination process, tub after tub is handed over from a magazine in the bio-decontamination chamber through a passive

Table 1: Overview of RTU transfer processes and criteria for selection decisions.

Criteria	No-Touch-Transfer	Electron Beam	Pulsed Light	Hydrogen Peroxide
Accessability of equipment and surfaces to cleaning and sanitization	Cleaning and desinfection procedures for the different machines to be established and validated	Manual cleaning of the inner chamber, automated bio-decontamination process (H_2O_2) for the last chamber	Automated bio-decontamination (H_2O_2) process for the pulsed light chamber	Automated bio-decontamination process for the H_2O_2 chamber/tunnel
Material flow	Tub commonly in double bag in grade C	Tub at least in single bag in grade C	Tub at least in single bag in grade C	Tub at least in single bag in grade C
Need for interventions by personnel	Glove interventions required if bags are folded incorrectly	Robust transport of tubs into class A without intervention	Robust transport of tubs into class A	Robust transport of tubs into class A
Frequency of interventions	Medium	Low	Low	Low
Complexity of process		Unwrapping / debagging in front of e-beam; cleanliness classes: grade C / unwrapping outer bag --> irradiation of outer tub surface --> grade A / tub opening	Unwrapping / debagging in front of pulsed light chamber; cleanliness classes: grade C / unwrapping bag --> grade B / decontamination with pulse light --> grade A / tub opening	Unwrapping / debagging in front of H_2O_2-deco-chamber/tunnel; cleanliness classes: grade C / unwrapping bag --> decontamination with H_2O_2, tunnel/chamber represents a material lock --> grade A / tub opening
Infrastructure requirement	High Space requirement for different machines: a) manual, semi-automated, or fully automated outer bag opening b) automated inner bag opening station c) automated tub opening, lid removal	High Weight of electron beam needs appropriate building structure; space requirements: a) manual, semi-automated, or fully automated bag opening b) Electron beam c) automated tub opening , lid removal	Medium a) manual, semi-automated, or fully automated bag opening b) Pulsed light decontamintion chamber; robotic c) automated tub opening, lid removal	Low (chamber), Medium (tunnel) Space requirements for tunnel; a) manual, semi-automated, or fully automated bag opening b) H_2O_2 decontamination tunnel or chamber c) automated tub opening, lid removal
Microbiological reduction	No reduction	Decontamination (6 log at 15 kGy) or sterilization (12 log at 25 kGy) [7]	Disinfection (reduction 4 - 6 log) - as per manufacturer's information [9]	Decontamination (reduction 6 log)
Impact to product	No impact	No or low residuals of nitrogen oxides and ozone at object level	Little or no oxidative atmosphere	Low H_2O_2 residuals in glass vials < 50 ppB
Complexity of validation	- Intensive airflow visualization study at mousehole to grade A - EM in transfer section	- Color strip dosimetry to be applied - Residuals study required for sensitive products	- Validation of microbial reduction using bioindicators - Residuals study required for sensitive products	- Validation of microbial reduction using bioindicators - Residuals study required for sensitive products
Health authorities acceptance	Accepted, but different interpretations of measures	Accepted	Not yet fully established	Accepted (H_2O_2 process for decontamination)

A safe transfer process with the appropriate technology will minimize risk. This is done with attention to every process step after sterilization of the packaging material at the supplier.

mousehole into the fill zone. That principle is also an example of "no-touch-transfer" from a nonclassified (but bio-decontaminated) section with HEPA-filtered UDAF into grade A, but this time in a closed setting with no operator access. A closed isolator setup is very much dedicated to small batches because storage volume and handling of nested components (e.g., snap-fit caps) is limited. This setup is also common with fast transfer H_2O_2 airlocks docked to the isolator or tubs hanging in the isolator during initial isolator bio-decontamination cycle.

AERODYNAMIC MEASURES WITH NTT

Airflow studies have been performed to show the aerodynamic situation in the last debagging and transfer step [18, 19]. One of these studies was published before Annex 1, in 2022. The other study was published in 2024. In the last debagging step, manual interventions should be avoided. However, in case unplanned interventions are necessary, they should follow the same SOPs known from interventions in the fill/finish environment with openly exposed aseptic products. The goal is to avoid any transfer of potential contaminants (e.g., particles, microbes) from the bags or the bag opening environment to the tub.

The article "No-Touch Transfer (NTT)" [19] demonstrates some of the difficulties in designing the airflow. Vertical UDAF meets horizontal overflow from the isolator (triggered by the pressure difference between the isolator and the debagging environment). Cutting equipment, flaps of the inner bag, and the tub front face present a barrier to the horizontal airflow, which leads to deflection. This could create a turbulent situation that might be limited by a thorough airflow design. Factors that could impact airflow include the velocity [20] and direction of the airflow coming from the HEPA filters above the debagger and leaving to the return air duct openings in isolators, airflow opening grids in a RABS, or the pressure difference between grade A (isolator) and grade B or C (bag opener).

RISK COMMUNICATION AND REVIEW

A safe transfer process with the appropriate technology will minimize risk. This is done with attention to every process step after sterilization of the packaging material at the supplier. These steps include incoming goods control, warehouse storage, cleaning and disinfection of debagging and transfer equipment, maintenance of

automation and cleanroom technology, robust recipe parameters, and trained interventions, if needed.

According to Annex 1, the central document for risk analysis and mitigation is the CCS [1]. It is the guide through the whole process for production management, operators, quality department, and authorities. A CCS is a living document with regular reviews [21]. It serves to document the decisions taken. Regular reviews will include results from continuous process verification and new measures taken as a result of effectiveness checks.

CONCLUSION

In this article, the different systems for RTU components have been described with technical details, advantages, and disadvantages. All systems described are in use in industry and have proven to be effective. It is up to the user to evaluate them for individual applications based on a sound risk assessment as documented in the CCS.

Table 1 gives an overview of NTT and re-decontamination processes that could be applied to RTU (tub system) transfers. The criteria listed address important aspects for decisions, but the list is far from covering all aspects of process design and capex criteria.

As already mentioned, the new Annex 1 strives for quality and availability of sterile medicinal products. In choosing cleanroom settings and transfer processes, microbiological aspects are only one side of the decision framework. Technical complexity and robustness of equipment, availability of skilled personnel, facility constraints, and affordability of solutions are further criteria to be evaluated for a well-considered decision.

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