PHARMACEUTICAL ENGINEERING®

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GAMP®+ AI

Applying GAMP® Concepts to Machine Learning

The Road to Explainable AI in GxP-Regulated Areas

What You Need to Know About *GAMP® 5, 2nd Edition*

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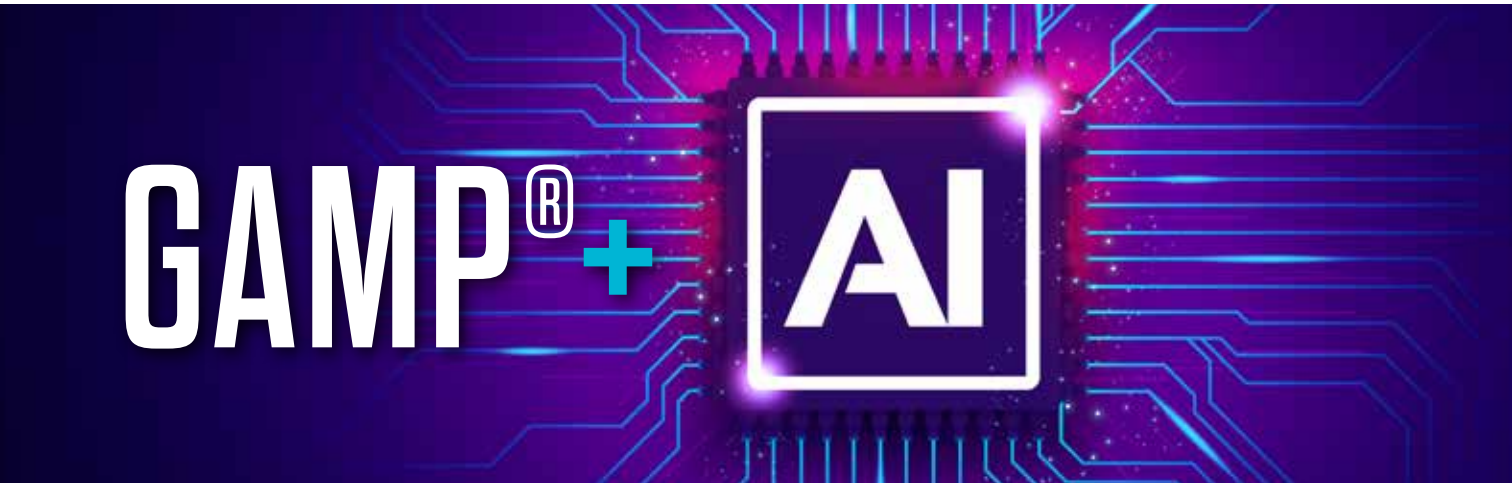

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24 THE ROAD TO EXPLAINABLE AI IN GxP-REGULATED AREAS

Recent advances in artificial intelligence (AI) have led to its widespread industrial adoption, with machine learning (ML) algorithms demonstrating advances in performance in a wide range of tasks. However, this comes with an ever-increasing complexity of the algorithms used, rendering such systems more difficult to explain. AI developments offer a solution: Explainable AI (xAI): i.e., additional modules on top of the AI core solution that are designed to explain the results to a human audience.

33 WHAT YOU NEED TO KNOW ABOUT *GAMP® 5 GUIDE, 2ND EDITION*

ISPE's *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* (*GAMP® 5 Guide, 2nd Edition*) maintains the principles and framework of the first edition and updates their application in the modern world, including the increased importance of service providers, evolving approaches to software development, and expanded use of software tools and automation. The 2nd Edition highlights the use of critical thinking by knowledgeable and experienced subject matter experts (SMEs) to define appropriate approaches.

ON THE COVER Abstract images illustrate the concepts of artificial intelligence and machine learning, which are discussed in several articles related to GAMP® in this issue.



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Senior Director, Editorial: Susan Sandler, ssandler@ispe.org

Technical Copy Editor: Heather E. Saunders

Publications Coordinator: Marcy Sanford

Advertising and Sales
Brad Ettinger, VP Marketing Communications & Business Development
bettinger@ispe.org

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

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

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

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

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By Michael L. Rutherford


Michael L. Rutherford

GAMP® Rings in the New Year

As we head into 2023, it is hard to believe that it has been four years since the COVID-19 pandemic started to impact our lives and transition us to a new normal. It is also amazing how much technology and innovation continued to advance in those four years to allow our industry to develop new vaccines and innovative products to meet the world's challenges.

This time has also resulted in major advancements in our ability to communicate, work remotely, and share information through improvements in computerized systems and infrastructure technology. The latter are the focuses of the GAMP® Community of Practice (CoP) and the theme of this issue of *Pharmaceutical Engineering®*.

GAMP is near and dear to my heart, although through my involvement in ISPE International, I know that ISPE is much more than GAMP as demonstrated by our numerous CoPs and technical conferences that highlight the amazing innovations within our industry every year. ISPE brings together a very diverse group of technical disciplines and expertise, which drives innovation within our pharma industry. These advances, not only in our industry, but in all aspects of our lives, have been heavily impacted by rapid changes in computerized systems and infrastructure capabilities and technology.

Almost everything we do these days, whether it is control systems for manufacturing equipment and technology, data acquisition, data management, data analysis, artificial intelligence and intelligent automation, supply chain management, medical devices, laboratory technology, and training and education programs, involves the use of computer and infrastructure technology and the cloud. Ensuring these systems function as intended is critical to ensuring the safety of our products and the integrity of the data we generate, which is what GAMP is all about.

ISPE brings together a very diverse group of technical disciplines and expertise, which drives innovation within our pharma industry.

GROUNDBREAKING GAMP

The GAMP CoP celebrated its 30th anniversary in 2021 and is one of the larger ISPE CoPs. The *GAMP® 5 Guide*, written in 2008, has been the leading industry guidance on computerized system compliance. The guide facilitates the interpretation of regulatory requirements and promotes a system life-cycle approach based on good practices. It also

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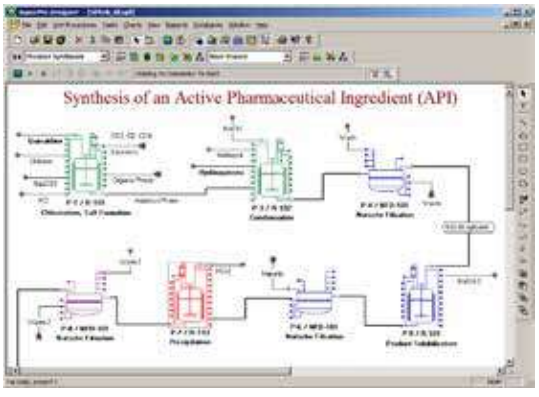

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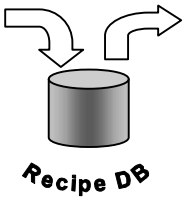

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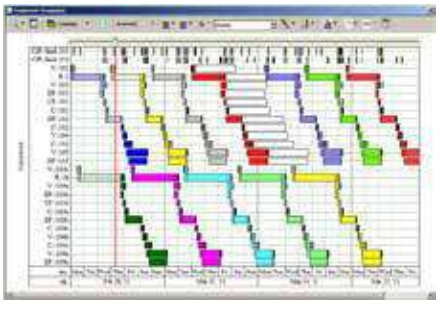

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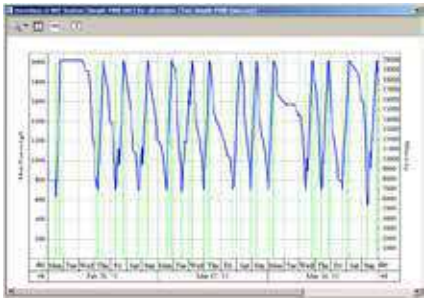

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SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor,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

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emphasizes the importance of the integrity of critical records, data, and decisions, as well as those aspects affecting physical attributes of the product.

While the *GAMP 5* framework and key concepts remained appropriate, current, and unchanged, and quality risk management approaches remained in place, an incremental revision was necessary to facilitate the adoption of more recent innovations. These included such innovations as Agile methodologies, cloud computing, automated tools, blockchain, artificial intelligence and machine learning, and open source software. To address these innovations and to remain current with industry trends, *GAMP® 5 Guide, 2nd Edition* was released in July 2022.

In September 2022, the US Food and Drug Administration released their draft guidance on "Computer Software Assurance for Production and Quality System Software," which described computer software assurance (CSA) and the various methods and testing activities that may be applied to establish it. (Comments on the guidance were due in November 2022; the final guidance is pending.) This guidance, which was under development for a number of years, reinforced the risk-based approach that *GAMP 5* had driven for more than 14 years.

GAMP® 5 Guide, 2nd Edition and the CSA draft guidance emphasize the use of critical thinking to strengthen the risk-based approach to computerized system life cycles, and encourage the application of patient-centric, risk-based approaches aimed at quality and safety, versus primarily compliance-driven approaches. They also focus on quality versus compliance as a critical emphasis for our industry and for ISPE because that focus ensures we are delivering safe, quality medicines and products to patients with the integrity in the data to support the use of those products. Enjoy this GAMP-themed edition of PE.

THE POWER OF VOLUNTEERING

One of our objectives in the 2023–2025 ISPE Strategic Plan is to improve the ISPE volunteer experience. ISPE is heavily dependent on our volunteers to provide technical content and resources for our members and professionals in the pharmaceutical industry in CoPs, committees, Chapters, Affiliates, projects, and conferences.

When I volunteered to present at a GAMP Forum in January 2003 and share content from a pivotal regulatory inspection, I didn't understand the impact that decision would have on my career, the support of ISPE's initiatives, and the influence that would have on our industry and ultimately on the patients we serve. That decision to "get involved" has led to some of the best, most rewarding, but also challenging 20 years of my ISPE life. It has helped shape my career and opened doors I had never considered. The network of industry professionals I have established, the colleagues and individuals I now call friends, the knowledge I have acquired and shared, and the impact those efforts have had on our industry and my area of expertise, are invaluable.

Yes, at times it does feel like a second full-time job as my involvement has increased with my participation on the International Board and Foundation Board, but you really get out of it what you put into it. For me, the benefits have far outweighed the time invested: a really good ROI.

The efforts of our volunteers often are not recognized outside of their specific CoPs, committees, Affiliates, and Chapters. So, in 2022, ISPE held a number of volunteer recognition events in conjunction with several of our key international conferences. These events celebrated the volunteers who helped ISPE provide technical resources to members and professionals in the pharmaceutical industry worldwide. The response has been very positive and provided another public opportunity to say thank you. Look for other recognition opportunities in the future as ISPE continues to improve the volunteer experience and encourages participation by our membership.

I encourage you to become an ISPE volunteer: get involved at the various levels of the organization and contribute to the future success of ISPE. You will be surprised what kind of impact it can have for you and the pharma industry.

Michael L. Rutherford is Executive Director, Computer Systems Quality and Data Integrity, at Syneos Health, and the 2022–2023 ISPE International Board Chair. He has been an ISPE member since 2003.



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By Zen-Zen Yen


Zen-Zen Yen

THE POWER OF A GROWTH MINDSET

When I started working in the pharmaceutical industry, I was looking for ways to grow my knowledge, my community, and my skillset. When I founded the Emerging Leaders committee within the ISPE D/A/CH (Germany, Austria, and Switzerland) Affiliate, I knew I had found that way.

ISPE and especially the Emerging Leaders (EL) groups around the globe have provided me with extraordinary opportunities for personal growth. I feel extremely honored to represent ELs globally as an ex officio member of the ISPE International Board of Directors. I'm looking forward to learning, unlearning, and relearning more.

Why? I believe our capacity for learning is becoming increasingly important. In the past, we learned how to do a job; in the future, learning will be the job.

In the past, we learned how to do a job; in the future, learning will be the job.

A GROWTH MINDSET

Someone who doesn't believe that they can keep learning new knowledge and skills has a fixed mindset, while someone who strongly believes that they are able to learn new things and improve themselves has a growth mindset. Never underestimate the power of the mindset. Lack of awareness is more dangerous than lack of knowledge; therefore, we should be aware of the importance of the growth mindset.

What's relevant today may become obsolete tomorrow. How can you learn in an area that was unthought of before? Because we are tapping into new areas almost daily, the workforce of the future will need to upskill and keep learning continuously, and fast.

"Becoming is better than being," said Carol Dweck in *Mindset: The New Psychology of Success*. We can all nurture our mindset to embrace growth and new challenges.

There are many ways that can help to foster a growth mindset, and many of these are available through ISPE.

Make Learning a Habit

Learning doesn't start or end with our profession. Making learning a habit helped me to stay curious and to keep looking for what's different or new. Being in a constant state of learning of course also means failing and starting again. More important, problems become challenges that want to be tackled.

There are unlimited ways to learn. However, it is important to identify the right way for one personally. Is it by learning from others, by experimenting, or by applying?

Embrace the Word "Yet"

Everything is in change constantly. So are our capabilities. The struggle we feel when starting something new can be discouraging. Facing the struggle of learning something new also means to normalize not being "good" at something yet.

By simply adding that "yet" to how we approach learning something new, we can allow ourselves to be within the process of gaining ability, valuing the process more than the actual result. Using "yet" can shift the perception of knowledge and learning from a goal to reach to an endless road of ideas.

Find a Mentor

Mentors have a unique opportunity to support their mentees in adopting a growth mindset through their role as advocate, coach, and champion. A mentoring relationship practically embodies the growth mindset. As a mentee, one needs to recognize challenges and growth opportunities to get the most value out of the relationship. As a mentor, one cannot assume to know all answers, but must focus on asking the right questions.

Finding a mentor can be difficult. I was very lucky that ISPE D/A/CH offers a mentoring program and that there are several mentoring circles within Women in Pharma®.

Zen-Zen Yen is Head of Engineering for Bayer AG and the 2022–2023 International Emerging Leaders Chair. She has been an ISPE member since 2016.

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By Vivianne J. Arencibia


Vivianne J. Arencibia

A LETTER FROM THE NEW WIP INTERNATIONAL CHAIR

As a woman of science, I can confidently say that I believe in magic. I believe in the magic that spurs from innovation rooted in desperation, necessity, and determination.

Over the last few years, the world has changed, and 2022 specifically, was a year of remarkable growth, evolution, and adaptation for the global pharmaceutical community. We embraced a new way of collaborating and problem-solving, moving the needle on our collective goal: improving patient lives worldwide.

It's fair to say that we—the pharmaceutical industry and members of ISPE—got the world back to normal, and as we work to adapt new technologies such as the MRNA vaccine to treat other life-altering ailments, we continue to improve society across borders. If that's not magic, I don't know what is.

MAKING MAGIC THROUGH WIP

So, as I said, I believe in magic. And if I could sum up my goals for 2023, it would be to bring that magic into the new year. I am confident this will be done with ease through ISPE's ever-expanding, ever-evolving Women in Pharma® (WIP) initiative.

As I assume the role of Chair for the Women in Pharma International Steering Committee, I look forward to the challenges and successes we'll undertake together. Like our industry, WIP continues to adapt, evolve, and grow, as demonstrated through WIP's most recent expansion. Just last year, we witnessed three new WIP groups emerge in Malaysia, Japan, and the D/A/CH (German, Austria, and Switzerland) Affiliate. This is incredible, and only enhances the WIP program's 2023 objectives: to elevate our international reach and to break down cultural and geographic barriers.

As we prepare for the coming months, we are excited to launch international engagement opportunities that support our four pillars: personal growth, professional growth, social impact, and Shaping the Future of Pharma™.

Taking on a more granular and collaborative approach to programming, we will generate content and educational resources that reflect the diversity of our member base. Our 2023 efforts will tap into regional developments and market needs while creating a space to better understand cultural nuances, best business practices, and market demands.

We continue to improve society across borders. If that's not magic, I don't know what is.

BUILDING ON THE MISSION

As we welcome a new Steering Committee and members new and old, we welcome new ideas and topics of conversation. Through WIP 2023 programming, you will walk away with confidence, leadership skills, emotional intelligence, and a comprehensive understanding of diversity, equity, and inclusion.

We look forward to building on our mission to empower women and take it one step further by providing a global stage so that they may share their brilliance and expand their impact. Together we'll work strategically, intentionally, and collaboratively to tackle unconscious biases in the workplace; connect women with mentors and mentees across cultures, races, and genders; and allow the WIP community to foster important partnerships and maximize workplace contributions. We look forward to sharing leadership stories, creating forums for exchange, and discovering new ways to position women as leading experts.

As we ramp up for 2023, we ask that you visit our website at ispe.org/women-pharma and sign up for our quarterly newsletter, *The Bridge*, to stay in the know about all WIP happenings. We encourage you to connect with the Steering Committee, WIP members, and your local Chapter and Affiliate WIP liaisons on LinkedIn for quick exchanges and information on upcoming events and opportunities. For program resources, head to ISPE Engage and explore the Women in Pharma community page.

Thank you for your interest in WIP and thank you for all you do.

Vivianne J. Arencibia is the Vice President of Global Quality Systems and Compliance with Moderna Therapeutics, Inc., 2022–2023 Secretary of the ISPE International Board of Directors, and 2022–2023 Chair of the ISPE International Women in Pharma® Steering Committee. She has been an ISPE member since 1991.



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APPLYING GAMP® CONCEPTS to Machine Learning

By Eric Staib, Tomos Gwyn Williams, PhD, and Siôn Wyn

This article explores life-cycle activities for machine learning (ML) within regulated life sciences. It positions and contextualizes the life cycle and management of the ML subsystem or components within a wider system life cycle. It also gives general descriptions and guidance illustrated by a case study demonstrating a ML application to medical image recognition, or software as a medical device (SaMD) [1].

This article focuses on the ML component or subsystem embedded within the wider system, solution, or application. It is not intended to be a general primer or introduction to artificial intelligence (AI) or ML, nor an introduction to general computer validation and/or life-cycle activities.

ML is a subdiscipline of AI. An ML system builds a predictive model from input (i.e., training) data, and uses the learned model to make useful predictions from new, never-before-seen data.

For most systems that use ML, many aspects of the traditional computerized system life cycle, and compliance and validation approach, are still fully applicable (e.g., those related to specification and verification of user interface, reporting, security, access control, data integrity, and data life-cycle management).

The use of the term *ML component* is not intended to suggest that such a component is a single entity. In most cases, the ML component will typically consist of several subcomponents comprising a "pipeline" supporting a number of functional stages, such as input/data preparation or output/results filtering, and one or more central ML "engine" or model(s) connected together. In such cases, the term *ML subsystem* is the most appropriate. The authors strongly encourage the use of appropriate software automation and other tools to develop and manage both the ML subsystem and the broader, overarching system, solution, or application. This article also seeks to avoid the implication that new documentation deliverables are necessary, unless they are clearly required by regulations (for example, in some cases of SaMD where device requirements, user needs analysis, human factors evaluations, clinical trials, and regulatory submission need to be considered), or such deliverables are clearly beneficial to the reliability, maintainability, and/or quality of the operational system and its fitness for intended use. (See the sidebar for other key definitions.)

Operational ML subsystems provide different outputs as they evolve, but the verification and validation of the system should be kept updated in line with these changes. This must include appropriate change management, version control, and monitoring. In addition, some ML systems have stochastic elements (having a random probability distribution or pattern), which means that results will be different for identical inputs regardless of model training. Therefore, validation and verification must use a sufficiently large validation data set and calculating summary performance measures that are meaningful and representative of the overall system performance and robust to small output variations between successive runs.

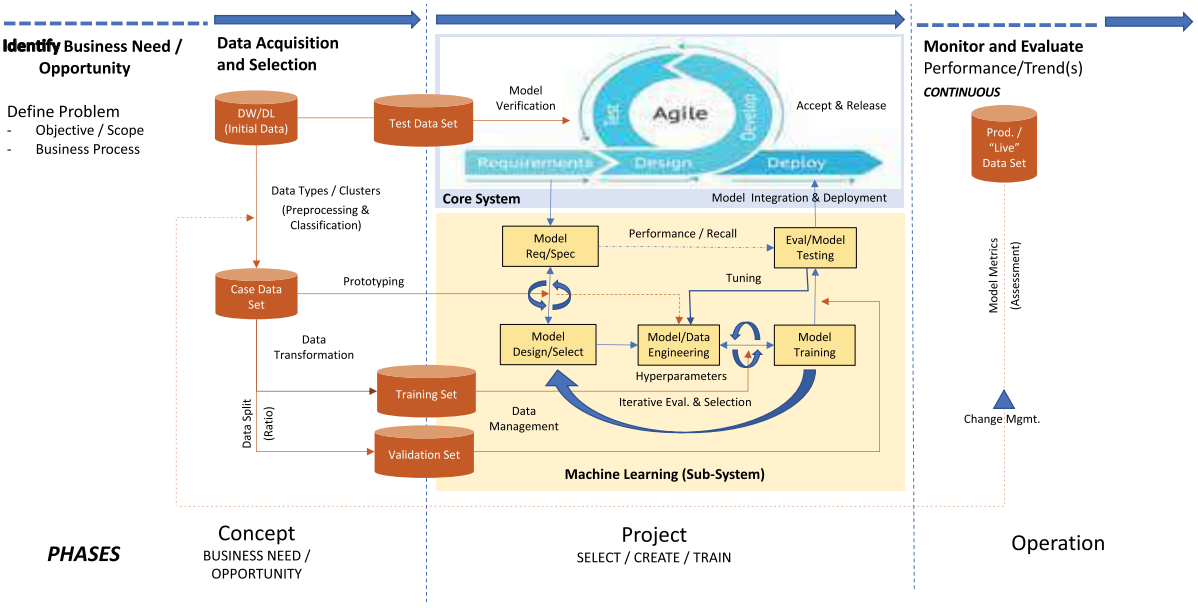
PREREQUISITES AND CONTEXT

There are many similarities in best practices between ML and more traditional algorithmic programming. Successful implementation of ML requires good business analysis and process understanding by data scientists, effective planning, and the application of good software development, engineering, and maintenance practices. The business case and intended use must be fully understood to best select the right data and data management must be supported by a mature data governance strategy.

Performance metrics are important in the design of any ML subsystem. They define what output(s) will be generated and how they will be evaluated against the required or expected results to determine the ML performance. These metrics drive the iterative training, evaluation, and improvement stages that are inherent within the development of all ML systems, as described in the project/production phase.

Another key aspect of ML development is the tight integration of data and metadata into the development process. The term

Figure 1: ML subsystem life cycle.



data-centric development is sometimes used to reflect this. As a result, data should be managed with utmost care, including controls for data acquisition, selection, classification, cleansing, and augmentation.

As with other software system development, ML development has business, technical, and project risk activities commensurate with the complexity and novelty of the system. Managing these risks require good process/business analysis, risk analysis, and cost/benefit analysis at all stages of development to recognize issues and decide whether to take mitigating or rectifying steps, or to terminate the project.

Development planning requires consideration of human factors or bias, privacy, security, and legal liability. This requires transparency and an understanding for the ability to reproduce outcomes, adequately interpret the results, and understand the applicability for how models will be applied.

The level of risk depends on the intended use. The extent, rigor, and documentation of validation and controls should take into account factors such as the level of human involvement, the significance of information to the healthcare decision (to treat or diagnose, to drive clinical management, or to inform clinical management), and the healthcare situation or condition, (critical, serious, or nonserious).

The ISPE *GAMP® Records and Data Integrity Good Practice Guide: Data Integrity by Design* [2], Appendix S1: Artificial Intelligence: Machine Learning, identifies the life cycle of data within a ML framework, emphasizing the link to both the GAMP data life cycle and GAMP system life cycle. Wider data integrity (DI) topics are also discussed in the guide.

ML SUBSYSTEM LIFE-CYCLE OVERVIEW

The following is an overview of the life-cycle model for the ML subsystem (see Figure 1). Phase terminology consistent with the GAMP 5 overall system life cycle is used including concept, project/production, and operation. A case study follows that presents the specific life-cycle activities for a SaMD product. For consistency with the *GAMP® Good Practice Guide: A Risk-Based Approach to Regulated Mobile Applications* [1], phase terminology includes project and production.

In the concept phase, the business need or opportunity is identified, clarified, and agreed upon. The specific problem to be solved is defined. The initial data is identified (it may be from a data warehouse or data lake), selected, and prepared as "case data." Prototyping allows the assessment and selection of suitable algorithms and hyperparameters, and preliminary hyperparameter values used to control the learning process. Examples are variables that determine the network structure, such as number of hidden units, and variables that determine how the network is trained, such as the learning rate. Data management begins in this phase when the case data is originally collected.

During the project/production phase, following a defined plan, the selected technologies and technical architecture are defined. Formal risk management activities commence, as well as other supporting activities, including project-based configuration and change management. Project/production phase activities for the ML subsystem are typically iterative and incremental rather than linear. These iterative activities include model design/selection, engineering, model training, testing, evaluation, and hyperparameter tuning.

Definitions

Artificial intelligence (AI): a system that displays intelligent behavior by analyzing its environment and taking actions (with some degree of autonomy) to achieve specific goals. AI-based systems can be purely software-based, acting in the virtual space, or can be embedded in hardware devices. As a scientific discipline, AI includes several approaches and techniques, such as machine learning (of which deep learning and reinforcement learning are specific examples), machine reasoning (which includes planning, scheduling, knowledge representation and reasoning, search, and optimization), and robotics (which includes control, perception, sensors, and actuators, as well as the integration of all other techniques into cyber-physical systems).

Machine learning (ML): a subdiscipline of AI and a program or system that builds (trains) a predictive model from input data (such as training data). The system uses the learned model to make useful predictions from new data drawn from the same distribution as the one used to train the model.

Deep learning: also known as deep structured learning or convolutional neural networks (CNNs), it is a part of a family of machine learning methods based on artificial neural networks with representation learning.

Random forest: a ML technique used to solve regression and classification problems.

Case data: data that is strategically selected to be unbiased and representative of the types of information to be processed by the ML, used for selection of training and validation samples/subsets.

Training data: a sample and/or subset of data, used for learning, to fit the model parameters of the model/classifier.

Validation data: a sample or subset of data used during model training and tuning to evaluate the model. The data provides evaluation independent of the training data, but not completely independent of the model training process. In data science and AI/ML, validation is used differently in GxP computerized systems.

Test data: a sample and/or subset of data excluded from all training, tuning, and validation activities, reserved to assess and evaluate the performance of a fully specified model/classifier.

Gold standard/"ground truth": a set of results that serves as the approved external criterion in which the model/classifier output is ultimately evaluated and/or compared against.

Data management is another key project/production phase activity, including the acquisition of new data, secure storage and handling, preparation (including labeling), and partitioning of data into training and validation data sets. During the model development stages, the training data set is used to train the model, and the validation data set is used to provide an unbiased evaluation of the model while tuning the model's hyperparameters. In certain scenarios, such as cross-validation experiments, specific data sets may fulfill the role of training and validation but not in the same iteration of the experiment. The test data set is excluded from all training and hyperparameter tuning activities; instead it is used to provide an unbiased evaluation of the final model within the overarching system. There is usually integration of the ML component into the wider computerized system and deployment into the target or other environment where acceptance and release activities are performed using the test data set.

In the operation phase, the system performance is monitored and evaluated. As new (live) data becomes available, further configuration/coding, tuning, training, testing, and evaluation are performed. There is likely to be a tight and iterative loop of alternating production and operation activities as the availability of new data and ongoing performance evaluation and quality checks lead to opportunities for improved performance, both proactive and reactive, or changing scope of use. This requires effective change and configuration management applied to all constituents of the ML system, such as code, the data, and models.

ML SUBSYSTEM LIFE-CYCLE PHASES

The following sections describe and discuss the typical activities conducted during the ML subsystem life cycle and are supported by an illustrative case study example [3] at the end of the article.

Concept Phase

The objective of this phase is to provide insight into the expected development cost and operational benefits of a ML subsystem. This should include a decision or rationale on why a ML solution shall be incorporated. This phase also provides opportunities to research and investigate which ML algorithms should be considered for development based on cost, development risks, and expected performance. This phase also

include efforts in gathering initial case data and understanding the properties of that data.

Identify business need and opportunity

The business need is developed and analyzed, the overall process and workflow are defined and agreed upon, and how the proposed application will support the process is identified. This analysis will help determine constraints, such as availability of data, deployment hardware, legal liability, and regulatory and intellectual property (IP) factors. Detailed data-related factors such as source, structure, format, and segmentation should also be considered.

Problem definition

At this stage, the initial set of requirements may be specified. This initial "requirements specification" drives the development and defines the functionality required from the system and ML subsystem.

Nonfunctional requirements such as integration and deployment constraints should also be considered at this early stage to inform the choice of ML algorithms. Nonfunctional requirements include an initial set of performance metrics. These are a detailed description of the ML subsystem output and how these outputs will be compared to the defined expectations. This comparison will provide quantitative measures of how well the subsystem performs. These measurements drive the training, evaluation, and tuning of the ML subsystem models. The performance metrics may change during development, training, and retraining. Other nonfunctional requirements include deployment constraints, such as choice of hardware, and performance constraints such as speed and/or capacity.

Prototyping

ML projects can benefit significantly from deploying algorithms and techniques developed for and applied to other applications and use cases. The objective of this stage is to conduct research and initial prototyping to identify which algorithms and resources are most likely to result in successful delivery of the project.

The ML field has a varied and growing range of algorithms and model architectures to choose from, and within each algorithm there are numerous hyperparameters to tune. For a new system, it is unlikely that the choice of algorithm is so clear-cut that a decision can be made to fully specify the component and proceed to development at this stage. In order to decide which algorithm is most suitable and how it should be trained and evaluated, the candidates should be evaluated against the operational, performance, and, if relevant, regulatory requirements. These activities provide an early indication of the likely predictive performance of the model and how likely the system is to achieve that level of performance.

Data acquisition and selection

An initial set of data will be collected from the existing business activities, or need to be gathered, to provide a starting point for the prototyping. Once identified, this stage determines what is required to prepare the data for the training and evaluation of the models, including formatting, cleaning, and feature extraction (collectively referred to as data transformation). It is also likely that the data needs to be labeled to provide the training inputs from which the prototype subsystem will be evaluated. At this phase, it is not expected that the data be complete because subsequent stages will identify if there is a need for additional data and the plan for acquiring and labeling that data. It is, however, important to partition the case data into training and validation sets to avoid compromising future evaluations. Training data may include biased human decisions or reflect inequalities, or bias may be introduced by flawed data sampling, in which groups or classes are over- or underrepresented in the training data. Appropriate measures should be applied to control the risk of such bias.

Project/Production Phase

The output from this phase is an implementation of the ML subsystem integrated into the overarching IT system together with extensive performance evaluation measures. Integral to this is the development of the training and performance evaluation infrastructure that supports training, tuning, and evaluation of the models. Tools supporting model construction or data preparation may also be developed during this phase (such as tools that support labeling of the training data).

This phase follows an iterative approach where successive versions of the ML subsystem are specified, designed/selected, implemented, trained, tuned, and evaluated. The phase consists of a series of experiments that iteratively improves the design, implementation, and hyperparameter selection of the subsystem to optimize performance.

Project data management

Prior to the project/production phase kickoff, it must be determined if the case data fulfills the requirements of the project life cycle: for instance, that there is a sufficient amount of data to train the model and a data range that encompasses the expected real-world data. If this is not the case, additional data will be needed, which may require a separate data acquisition project. This phase also determines the appropriateness of the data for intended use, and prepares it for subsystem development. Activities include format specification, selection, and application tools for data annotation and clean up.

The extent and format required for the data is driven by the performance metrics previously obtained. For example, for the task of image analysis object localization, the performance metric is specified as the agreement between the ground truth and results predicted by the AI. The ground truth is the set of results that serves as the approved external criterion in which the model/classifier output is ultimately evaluated and/or compared against. To achieve this, the ground truth data and AI output must be in a comparable form that will enable that measurement to be made (for instance, by image segmentation). For a classification task, simple labeling of an image as containing a particular feature may be sufficient.

Model requirements specification

This stage may be considered a "tollgate" in the project/production phase, where information gained from the previous phase is documented and presented together with informed and detailed planning for the project/production phase. The objective is to provide information on the likely cost, risks, and benefits of the ML subsystem to inform a decision on whether or not to continue. The information presented during this stage provides confidence that the additional investment required in data acquisition, management, and development will deliver the business need.

The information and experience gained during the concept phase are utilized at the start of the project/production phase to specify and design the ML subsystem to as much certainty as possible and allow for the planning effort, including risk estimation, of its delivery. Activities in this stage include formulating the initial design of the subsystem by identifying the main components and how they will integrate to perform the analysis. Design decisions rely heavily on the practical experience gained in developing the prototype solutions in the previous phase. In addition, the specification of the subsystem is formed, which includes the format of the input and output data for the subsystem and the definition of performance metrics.

Planning involves detailed breakdowns of the development effort with estimates of timelines and associated risks. Risk analysis of the project can be performed during this stage to determine the items most likely to fail and provide for appropriate mitigating actions or alternative solutions to reduce risk. Planning also includes the specification of the development environment for the ML subsystem, which will have its own budgetary implications in the form of software licenses and computing and storage resources. The development operations and hardware infrastructure are set up to support the ML component training and evaluation. These may include code and data version-controlled repositories, applying any combination of local and cloud-based computation. This phase may use a research-focused language and platform, but should also take into consideration the end deployment requirements and platform to ensure that there are no subsequent technical or IP infringement issues.

Model design and selection

The baseline architecture of the ML model is chosen and designed during this stage. Knowledge gained from the prototyping phase is applied here to identify the single or small number of candidate algorithms identified as being most likely able to fulfill the model requirements, both functional and nonfunctional (such as performance). The requirements can be sufficiently broad to allow the selection of models across different ML algorithm classes. Data scientists should be wary of choosing too many candidate algorithms at this stage since the effort required to optimize each can be significant. If the number of candidate algorithms is greater than three, the scientists may wish to return to the prototyping stage to eliminate some to avoid excessive optimization.

The choice of the underlying ML algorithm leads to the set of hyperparameters for each model. Subsequent iterations of the development process refine the architecture driven by model test results.

Model/data engineering

This stage involves constructing the model architectures and the surrounding infrastructure for data input and evaluation that enables training and hyperparameter tuning of the models. Tasks include selecting, preparing, managing, and maintaining the data for training iterations and recording results to allow comparison between trials of different hyperparameters and results from different versions of the architecture. Once set up, the infrastructure is then employed to execute a series of trials in which the model hyperparameters are altered to determine the set of parameters that result in the best model performance.

Model training and hyperparameter optimization

This stage involves training a series of model instances by varying hyperparameter values (e.g., the number of hidden units or learning rate) and recording the results. Hyperparameter optimization may involve manual selection and altering the parameters after each iteration, or automated processes using exhaustive search or the more efficient Bayesian optimization of the hyperparameter space.

Most ML algorithms possess many hyperparameters and hence define a large hyperparameter space over which to optimize. However, applying knowledge of the algorithm and problem domain gained during the prototype phase allows data scientists to identify the subset of hyperparameters whose values can be predetermined and fixed, thus greatly reducing the parameter space. Though libraries and infrastructures exist that allow for automated hyperparameter tuning, data scientists are advised not to take a completely hands-off approach to hyperparameter tuning. Dividing the hyperparameter search space experiments into smaller regions by allowing only a subset of the hyperparameters to optimize for each experiment run can provide useful insights on the effect hyperparameters have on the model training and performance, leading to a more efficient tuning stage.

The output from this stage is a trained model using all the training data and an optimal, or near-optimal, set of hyperparameters. This is considered the best model given the existing fixed architecture and parameters evaluated using the validation data. The iteration of model design to model engineering to hyperparameter tuning to model training to model evaluation reveals insights into the performance of the latest and previous models. This yields further evidence as to how the model architecture and training options may be altered to improve the performance and then a redesign or selection of an alternative model may be performed and evaluated.

Evaluation and model testing

This is when the best-performing models from the previous training and selection iteration are subjected to the validation data. Excluded from the training of the previous iteration, the validation data is passed through the model(s) and the model's

performance is evaluated. A key requirement for a fair comparison is to apply identical training and validation data sets to each candidate model. The results are compared to the gold standard labeling to produce a set of aggregate and indicative performance metrics, or scorecards, which inform on the current performance and drive the following iteration if required.

Many ML libraries incorporate the validation data evaluation into their training functions, thus automating much of this process. Data scientists, however, should be wary of relying on the quantitative measures for model evaluation. Visual qualitative evaluation of the validation results often leads to better insights on how the model is performing, allowing common error modes to be identified/addressed, and enabling crucial refinement of the performance metrics to provide better alignment with the required outputs. To this end, it is advisable to use expert and domain knowledge when hyperparameter tuning, rather than relying solely on fully optimized hyperparameter tuning functions provided by many development environments. In practice, this will involve a hybrid approach consisting of a series of tuning experiments where a subset of hyperparameters are tuned according to a performance metric, interleaved with manual interpretation and qualitative analysis of the results, to determine the next set of tuning experiments or to terminate the tuning activities.

A detailed description and evidence of the performance evaluation and comprehensive performance measures of the pre-released product is a data science-based expectation.

When target model performance is achieved and/or no further changes to architecture are identified, the best performing ML models are selected as the candidates for integration into the overarching IT system and deployed. This selection is based on not only the nonfunctional requirement of performance on the validation data set, but also on the criteria defined in the requirements, such as the ease of algorithm maintenance, ease of deployment in the target deployment environment, and other nonfunctional requirements such as runtime.

Model integration and deployment

During this stage, the ML algorithms and models are migrated from the development environment code, which supports fast prototyping and experimentation, to deployment target code that is more efficient and more suited to deployment environments and long-term maintenance. This process involves removing much of the code designed to support prototyping candidate algorithms and experimentation. This includes identifying the parameters and algorithm choices to be adopted and removing candidate algorithms that did not yield the desired properties or performance.

Key to this phase is modularization to isolate the inference module of the code from the remaining code. Inference modules are the components of the code relating to the forward passing of the test or previously unseen data as input through to the output of the ML subsystem. Inference refers to the forward pass execution of the subsystem, the module of the code that accepts the raw data as input and provides the output. This excludes any function relating to validating the output against the ground truth, or code involved with altering the model parameters or hyperparameters.

> As with other software system development, ML development has business, technical, and project risk activities commensurate with the complexity and novelty of the system.

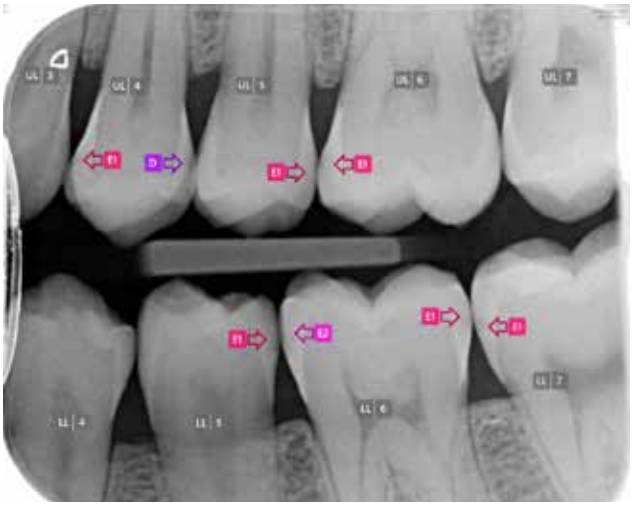
ML algorithms are typically developed in development environments tailored to support training, experimentation, and hyperparameter tuning. These environments are not always consistent with the deployment requirements, in which case porting the code and trained ML models to a runtime environment is required, along with the appropriate code review, verification, and testing. If necessary, the minimum amount of code that requires porting to the runtime environment is the inference portion. Integration also requires the specification and implementation of the interface between the ML subsystem and overarching IT system.

Similar to the inference, components of the pipeline performance evaluation exist in the training codebase. However, this needs to be implemented as a full pipeline performance evaluation, with the possibly to port it to a more suitable development and/or runtime environment.

Acceptance and release

The final infrastructure for release, maintenance, and performance verification of the ML subsystem is developed during this phase. Processes relating to the development, release, and maintenance of the subsystem is defined to specify if, how, and when the functions of developing ML algorithms are verified. Choices must be made as to whether the training and possibly tuning of the ML models are included in these processes. For example, it may be decided to run the complete model training, hyperparameter tuning, and model performance on the test data at regular instances to verify functions of the code. Alternatively, it may be deemed that the model training and hyperparameter tuning are not part of the core code or infrastructure, and are excluded from the verification process. At a minimum the process should specify, and appropriately document, how verification of the ML subsystem shall be performed. The execution of such processes should result in the release of the first version of the ML subsystem.

Figure 2: The product's graphical user interface [3].



Operation Phase

During this phase, the ML subsystem is continuously monitored and maintained. This may involve automation to alert if results deviate from predetermined limits, or may involve manual monitoring, or a combination. Performance monitoring may result in required changes affecting the subsystem. This is where the maintenance and performance evaluation processes need to be robust and sufficient to support the retraining and adoption of an alternative ML model(s). Such changes must be made in adherence with the organization's change management process, leveraging risk-based evaluation(s) considering the change's impact to current and future production data.

A typical request might be that the system is poor at generalizing to a specific subclass of input data. A typical solution is to acquire and integrate data of this subclass into the training dataset. The integration of additional training data must be systematic in that every change in the performance is measured, validated, and understood. For example, upon acquiring the additional data, a portion of it could be assigned to the training set and the rest excluded from all model training activities. Model training would proceed with the augmented training data set with the realization that the additional subclass of data may result in an overall drop in performance due to the inclusion of more challenging data. Once trained, tested, and tuned, performance of the revised model should be staged by initially executing the evaluation processes with the original model on the augmented test data set with an expectation that the performance may drop because of the increased challenge. Then, execution of the evaluation process with the revised model will take place with the expectation that the performance measures achieve the desired acceptable level.

It can be seen from this example that operation and maintenance of the system and ML subsystem are themselves iterative processes that follow the train-test-tune cycle of the original development effort, with appropriate management of new data through defined data governance and continued performance evaluation.

Case Study

This case study describes the development of an application for chair-side analysis of dental bitewing X-rays. Bitewings X-rays typically show both upper and lower teeth, including the root on the left or right side of the mouth. They are used as an aid to diagnose and monitor several conditions such as gum disease and cavities between teeth. The bitewing X-ray is taken by placing a sensor inside the mouth between the teeth and tongue, and pointing an X-ray source from the outside of the mouth. The sensor is then removed and digitally scanned to provide an image. Radiographic examinations can increase the number of carious lesions that are detected over those that would be detectable by clinical examination alone; this use is recommended by the UK Department of Health in the FGDP (UK) guideline document [4]. Nevertheless, systematic reviews have consistently reported poor diagnostic sensitivity of only 37% for radiographic detection of demineralization by dentists [5].

"The purpose of the product is to detect the early stages of tooth decay, known clinically as caries. Early caries are indicated by subtle changes in the appearance of the outer enamel surface of the tooth in bitewing x-rays. These small changes are challenging to detect, particularly given poor lighting conditions and time pressures present in a working dental practice. Not finding early-stage caries is a missed opportunity for using preventative treatments, such as interdental cleaning and resin infiltration, and is likely to lead to further decay and the need for restorative treatments such as drilling and infiltration" [6].

The product deploys a series of algorithms to analyze bitewing for early decay and highlights areas that merit a closer look by the dentist arrows indicated regions where the AI has detected image biomarkers that are indicative of early caries. Control in the graphical user interface allow dentists to move, delete or add arrows [3].

The product is provided in multiple forms: as a stand-alone application, integrated into the dentist's existing image management software, or a web-hosted analysis service. Under the EU Medical Device Directive [7], it is registered as Software as a Medical Device of class 1 safety to be used by qualified dentist practitioners to aid in the diagnosis of early enamel-only caries. The product is developed and released according to ISO 13485 standards.

The business opportunities and health benefits for an early caries detector are in minimal-intervention or minimal-invasive dentistry. This is a pioneering approach to dentistry where early preventive actions are favored to preempt and minimize the use of traditional drill and fill treatments. Thus, instead of waiting until the caries or decay has penetrated deeper into the tooth to merit drilling, the disease is detected early when decay is limited to the outer enamel surface, so it can be repaired by noninvasive treatments such as high-fluoride toothpaste or a hygienist visit [8].

The product's functional requirements were formulated to describe an assistive tool that highlights evidence of decay for

better-informed decisions on diagnosis and treatment paths. An assistive diagnosis function was chosen to dovetail into the dentist's existing work path. The assistive nature also had regulatory safety class implications in that the product can only be used by trained clinicians who are always given the final decision on diagnosis and treatment path. A key requirement for the product was that it provided clear indications to allow the clinician to make better-informed decisions but did not attempt to get in the way, otherwise interfere with, or replace the clinician's actions.

The product was also required to fit seamlessly into the dentist's clinical workflow. Once the need for a bitewing had been identified, the workflow involved acquiring a pair of bitewings, one for each side of the mouth, and analyzing the X-ray immediately on their chair-side computer so that patients could be informed of the chosen treatment path immediately. Note: Typically, dentists have only a short time to analyze each bitewing during which time they look for a range of conditions in addition to early caries. To this end, a fully automated analysis was required that highlighted regions of the bitewing that were early caries.

Nonfunctional requirements included working on a chair-side computer, usually a PC without specialist hardware or reliance on an internet connection. The analysis time also needed to be fast and not add to the dentist's current image analysis and clinical reporting time of 20 seconds.

Regarding caries detection performance, previous research demonstrated that general practice dentists detect approximately 40% of early caries [9, 10]. The performance objective was to increase detection rate without an unacceptable increase in false detections (i.e., false positives). False detections are undesirable, but since treatment paths are noninvasive, they were not harmful to patients.

A comprehensive search for relevant literature and published material on technologies relating to image analysis of dental bitewings was performed, with focus on evidence of implementation and performance. This yielded information on the application of deep learning algorithms to the analysis of dental images, but there were no published case data on bitewings. The lack of a significant published data set indicated the need for data acquisition to be conducted as part of the project, and thus a requirement that the ML algorithms used should not need a large sample size to generate a predictive model with suitable accuracy.

A task was undertaken to acquire an initial set of data which consisted of 130 bitewings collected from a single site (i.e., dental office/practice), selected to have higher prevalence of proximal caries. At the onset of the project, it was decided that for general dental practitioners to gain maximum benefit, the product would have to mimic the analysis of experts in dental bitewings. (Maxillofacial radiologists are the clinical experts in analyzing dental medical images and are adept at finding early enamel-only proximal caries in bitewings and distinguishing them from other pathologies or image artifacts.) To this end, five dento-maxillofacial radiologists were recruited; each one analyzed every image and recorded the location of proximal caries together with the severity

This case study describes the development of an application for chair-side analysis of dental bitewing X-rays.

of the caries on an internationally recognized four-point grading scale. Consolidation of the experts' analyses provided a single "gold standard" data set.

Due to the challenge of finding small pathologies in X-rays, the ML subsystem was designed as a pipeline of algorithms to utilize the larger features of the images. This prototype formed the backbone of a simple, interactive product demo, which allowed business collaborators and potential customers to provide images of their own as inputs and evaluate the results. This provided valuable user feedback to guide subsequent development. It also demonstrated the need for the solution to be generic to images from all acquisition hardware, hence the need for the project to collect general practice data (which occurred during the project/production phase).

The prototype performance report contained detailed descriptions of the training and evaluation methods together with all experiments executed with quantitative performance measures and qualitative evaluations, including illustrations of the failure modes. This report also included a considered prediction of the performance of the product. (Intellectual property analysis determined the freedom to operate and identify novel IP to be considered for protection.)

Results from the prototype demonstrated that the algorithm performed poorly on X-rays collected from other sites. A subsequent ethically approved clinical data collection project was initiated to collect images from 10 general dental practices and have them annotated by a panel of maxillofacial radiologists. Once collected and annotated, a test set consisting of 20% of the images was selected by random selection, stratified over the sites that were excluded from all training and validation of the models and evaluation of the pipeline to provide the unbiased data set for evaluation of the final ML subsystem and end product.

Based on the prototype experiments, the ML subsystem design in the case study consisted of three distinct components: (a) pattern recognition tooth detector; (b) identification of a superset of candidate locations of caries by dynamic programming; and (c) deep learning model for classification of candidates as either early caries or other. Risk analysis of these components identified the final stage as being the highest risk due to the more innovative approach of using neural networks compared to pattern matching and the potential need for a large training data set to ensure

sufficient detection performance. To this end, mitigating strategies were developed, such as identifying less data-hungry alternative classifiers or acquiring additional data.

The tooth detector and caries classifier both contained ML models, but for brevity we describe the planning for the final component: the deep learning classifier. The Python language and development environment was chosen to develop the deep learning classifier due to its support for rapid prototyping of ML models and availability of third party, convolutional neural network support libraries.

The data format was specified for each component. Focusing on the final component, the input was a set of candidate locations along the proximal tooth edges generated by the preceding component as indicative of caries, with the output specified as a probability of measure for whether a candidate is classified as having caries. These candidate locations and confidence measures could be evaluated by comparing them to the expert gold standard of caries annotations. The model's output was classified as true positives if they resided on the same proximal edge as an expert's caries annotation within a distance tolerance. This allowed for the construction of a receiver operator characteristic (ROC) curve accumulated for all candidate locations and for all potential threshold values, with the area under the curve (AUC) used as the principal performance metric for evaluating and comparing model performances.

For the task of object detection of early caries on the proximal edges of teeth, two candidate machine learning algorithms were identified: (a) random forest classification and (b) deep learning classifier.

Both required input data as a set of candidate locations along the surface edge. Ground truth data consisted of a classification if each point was non-carious or carious with a subsequent subclassification of carious regions as being enamel caries (i.e., caries that had only penetrated the outer enamel of the tooth) or dentine caries (i.e., caries that had progressed further into the tooth dentine). The performance metric was determined as the area under the ROC curve for the classification of enamel caries.

Model development followed the regular ML life cycle of iterative training, testing, evaluation, and hyperparameter tuning. Five-fold cross-validation stratified over the image source sites was used to divide the data into training and validation data sets. The approach for hyperparameter tuning involving careful recording of hyperparameters and results for each iteration was to manually identify the changes that had a positive effect on the performance and tweak the parameters accordingly for the next iteration, comparing performance metrics and performing qualitative evaluation of the results.

As the experiments progressed, it became evident that the deep learning classifier solution offered superior performance to the random forest classification and focus turned to choosing the best hyperparameters for that model.

The product specification required running the product on a regular PC without internet connection or bespoke hardware or additional software. To fulfill this nonfunctional requirement, the inference module of the ML subcomponent developed in Python was ported to C++ components of pipeline augmented with .net API. It excludes all modules related to evaluation, model training, and hyperparameter tuning. Deep learning models were ported from Python (TensorFlow) to ONNX format and runtime inference code written in C# using Microsoft ML support libraries. All design, maintenance, and release activities of the product were audited against ISO 13485 standards.

For the product, in addition to the inference module, code to validate the performance of the runtime inference was ported to the build and test pipeline environments. This enabled automated testing and validation of the model performance during the code build cycle. A design decision was made to develop a fully integrated performance evaluation reporting into the testing and release process. The interface was augmented with the ability to supply test images and compare the results with the gold standard annotations. Selenium UI testing was used to drive the tests which were integrated and automated in the testing components of the release pipeline. Model training and hyperparameter tuning functions were not considered core to the product and were excluded from the software maintenance and performance validation processes.

To provide additional validation of the product's performance, an ethically approved clinical study to investigate whether the ability of dentists to detect enamel-only proximal caries was enhanced using the product. The study reported that dentists using the product found 75.8% of the early caries compared with only a 44.3% detection rate for dentists using the bitewing X-ray image without AI assistance, a statistically significant increase in sensitivity of 71% [3].

During the study and subsequent early adopter usage, the need to train and educate users to gain maximum benefit from the product became evident. This type of interactive AI system, where the clinician is an integral part of the AI workflow loop, requires the human to examine the regions of interest suggested by the AI system but not blindly accept them as truth. Instead, users applied their clinical knowledge and judgment when making diagnostic decisions. Training material was produced to present users with the specificity and sensitivity performance measures of the product and discussions on how to best interpret the output to enable dentists to make better diagnosis and treatment decisions for their patients.

CONCLUSION

This article explored life-cycle activities for ML components or subsystems in regulated life sciences using an example of a SaMD product. It has illustrated the life cycle and management of the ML subsystem or components within a wider system or application life cycle. Such usage of ML is occurring throughout the pharmaceutical life cycle from drug discovery and clinical development, to post-licensure product surveillance and real-world data analytics.

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About the authors

Eric Staib is the Vice President of Compliance and Quality Management at Signant Health. He has more than 23 years of pharmaceutical industry experience in various GXP areas, including direct experience and leadership for quality systems development/management, software quality engineering, information technology, and computer systems validation. He holds a BS in biology from James Madison University, an MS in quality assurance and regulatory affairs from Temple University, a graduate certificate in project management from Lehigh University, and an MBA in pharmaceutical management from Drexel University. Eric was a previously Chair of the GAMP Americas Steering Committee for ISPE, and currently chairs a Software Automation and Artificial Intelligence Special Interest Group (SIG). He has presented at numerous industry conferences in addition to having published and contributed to several concept papers, magazine and journal articles, and good practice guides. Eric has been an ISPE member since 2001.

Tomos Gwyn Williams, PhD, is the Chief Technical Officer of Manchester Imaging Ltd., and leads research and development activities. Manchester Imaging specializes in the research and development of machine learning algorithms and their deployment in software as medical device products for both in-house and as third-party providers for other companies. Tom has over 20 years of experience working in artificial intelligence and machine learning spanning both academic and commercial institutions. He specializes in inventing computer vision solutions that aid clinicians in diagnosis and treatment planning and has developed successful solutions for a range of medical conditions including dental decay, nonmelanoma skin cancers, facial paralysis, and osteoarthritis. Tom has an engineering degree from Imperial College, London, and a PhD in AI from the University of Wales, Aberystwyth. He has been an ISPE member since 2020.

Siôn Wyn, Director, Conformity Ltd., is an acknowledged expert in computer system validation and compliance, data integrity, electronic records and signatures, and international regulations in this field. He assisted the FDA as a consultant with its reexamination of 21 CFR Part 11 and was a member of the core team that produced the FDA Guidance on 21 CFR Part 11 Scope and Application. He received the FDA Group Recognition Award for work on Part 11. Wyn is the Editor of ISPE's *GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems*, *2nd Edition*, co-lead of the ISPE *GAMP® Guide: Records and Data Integrity*, and is a member of the ISPE GAMP Global Steering Committee, GAMP Editorial Board, and the GAMP Europe Steering Committee. Wyn received the 2006 ISPE Professional Achievement Award, which honors an ISPE member who has made a significant contribution to the pharmaceutical industry. He received the ISPE UK Fellow Award in 2016. He is a Technical Consultant to ISPE.



THE ROAD TO EXPLAINABLE AI
in GxP-Regulated Areas

By Elias Altrabsheh, Martin Heitmann, FRM, Patrick Steinmüller, and Bruna Pastori Vinco

Recent advances in artificial intelligence (AI) have led to its widespread industrial adoption, with machine learning (ML) algorithms demonstrating advances in performance in a wide range of tasks. However, this comes with an ever-increasing complexity of the algorithms used, rendering such systems more difficult to explain [1]. AI developments offer a solution: Explainable AI (xAI): i.e., additional modules on top of the AI core solution that are designed to explain the results to a human audience.

The audience of xAI may be a human operator during runtime, a quality assurance team (QA), or in an audit context. The use of xAI can help address the algorithmic complexity of AI, which may lead users and subject matter experts as well as stakeholders from QA functions to find it difficult to comprehend the solution's decisions. This hinders acceptance and puts the potential benefits at high risk of never being deployed [2], which in turn causes impediments on innovative projects themselves.

Current regulatory initiatives also hint at interest in xAI, such as the European Union [3, 4] and the US Food and Drug Administration guidance [5] addressing concepts of trustworthy AI and human-machine interaction.

In this article, we elaborate on the benefits and requirements on xAI from a GxP point of view, along with the development and production process, with a focus on strategies to ensure that the intention of use is met and to manage risks for safety that arise from xAI itself. For effective operationalization, we suggest creating a roadmap to xAI in GxP regulated areas that integrates crucial stakeholders during the life cycle of the AI application regarding xAI design, development, and control.

We provide a structured, generalized way on how to design explainable AI solutions along the product life cycle to ensure trust and effectiveness in productive operation regulated by GxP requirements. We aim for GxP compliance of the explainable AI "add-on" itself, as it will fall under the same regulatory requirements when used in a safety-critical environment.

We continue our discussion from previous *Pharmaceutical Engineering*® articles about the AI maturity model [6] and the AI governance and QA framework [7]. Those articles introduced the concepts of autonomy and control in order to determine the target operating model of an AI solution and a development and QA governance framework, reflecting the evolutionary nature of data-driven solutions. Building on these concepts, we provide insights and guidance on how to effectively support the "Human-AI-Team," a term of the FDA [5] we believe describes very well the target operating model when interacting with AI: in a collaborative manner, complementing the strengths of cognitive as well as AI in GxP-related areas. We provide further details to the general approach to GxP-compliant AI as outlined in ISPE's *GAMP® 5 Guide, 2nd Edition* [8], especially in Appendix D11.

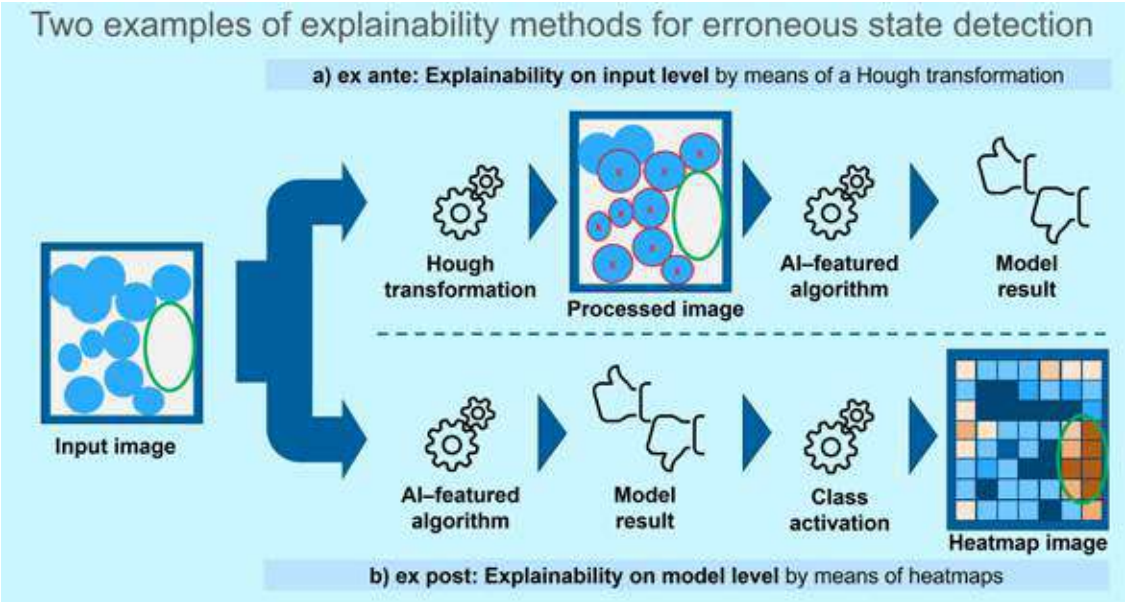
The article discusses:

- The black-box dilemma of AI applications: An example case to demonstrate how the complex nature of AI applications may hinder trust and operational agility when not complemented by xAI
- Needs and responsibilities for xAI across corporate functions: Elaborating on how the core business functions may support overcoming the black-box dilemma
- The road to xAI along the product life cycle: The road to xAI in a GxP context, i.e., an organizational blueprint to integrate corporate functions with their needs and responsibilities
- Guidance to measure effectiveness of xAI: For the specific aspects of validation, we provide guidance on how to set up an xAI test plan

THE BLACK-BOX DILEMMA

Imagine an AI-featured application that is clearly superior to existing rule-based computerized systems in a production

Figure 1: Explainability is the key to balance AI's complexity with understanding of the model output by all relevant stakeholders.



process, e.g., applying a monitoring system to determine erroneous states of critical production steps. The introductory case is inspired by the study "Preselection of Separation Units and ML-supported Operation of an Extraction Column" [9]. In our case, superiority entails an earlier detection of erroneous states and therefore, a measurable reduction in downtime, leading to a better adherence to quality expectations of our product. Another assumption in our case is that we were able to show this performance in a test or retrospect simulation setting by statistical measures, e.g., when comparing potential downtimes with and without our AI application in place.

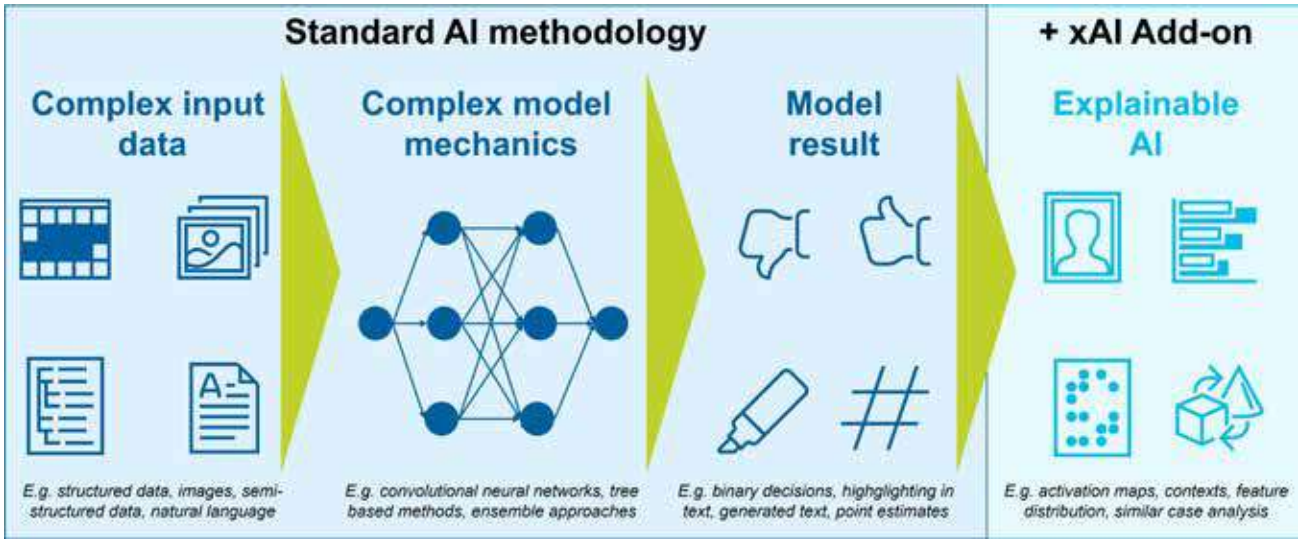
Despite the quantitative outcomes as sketched above, we must think about the context of use and the stakeholders interacting with the solution. The stakeholders may deem the application as "black-box," i.e., they might not be able to interpret its results, even if they acknowledge AI's performance in a statistical sense. In more detail, we may face the following impediments that arise when typical stakeholders in GxP context are not able to link the application's results with their respective mental models:

- Daily operation view: Users may not trust the solution's indications for erroneous states. From a user's point of view, this scenario is fully comprehensible since superior predictive power is only possible if formerly applied systems produced more false positives or false negatives than the AI alternative. Hence, notifications of the new solution will be surprising, especially when users lack understanding of why the notification has been raised. In another adverse scenario, users may blindly trust the AI solution, even for erroneous indications.
- Validation and QA view: The QA function must carefully monitor incidents raised by human operators or the automated quality control functions. In doing so, a conclusion must be reached whether the process is under sufficient control or whether further measures must be taken, yet with only the incident events as well as the complex input data and algorithm at hand, the clustering of information and the identification of root causes will remain difficult, requiring further ML engineer analysis. This itself can be seen as a case-to-case explainability analysis, yet in a less controlled and streamlined manner. It can also drive up costs.
- Product management view: Management will push to resolve interruptions in the production process as quickly and safely as possible, yet operating procedures may require deeper analysis, involving further parties and hindering the actual production process and the product release itself.
- Audit and regulatory view: Audit will require the process to be in full control with regard to safety and quality expectations. This must be demonstrated by the corporation that utilizes the AI solution, which is typically a QA team's duty. However, within a black-box environment, analysis and decision-making processes might take longer and so the responsiveness to critical situations might be under question.

With existing processes still in the lead with respect to GxP compliance, the consequences mentioned here contribute to why some AI solutions remain in pilot phase, and their quantitatively shown superiority will remain unharvested. And even if such a system would be applied in production, controls and double-checks might dilute the benefits from an economic point of view, on top of regulatory risks during audit.

So how can we overcome this dilemma? Explainable AI aims to be an add-on to the actual model engine that is designed to show stakeholders how AI has come to its conclusion (see Figure 1). The black box will be opened to a level suitable for the audience, and

Figure 2: Examples of the application of explainability in the introductory example AI case.



Management needs to make educated decisions on whether the risks involved in productive operation are outmatched by the operative and patient-centric benefits, balancing the business and the product quality perspectives.

along the way, the development process itself will benefit from these insights.

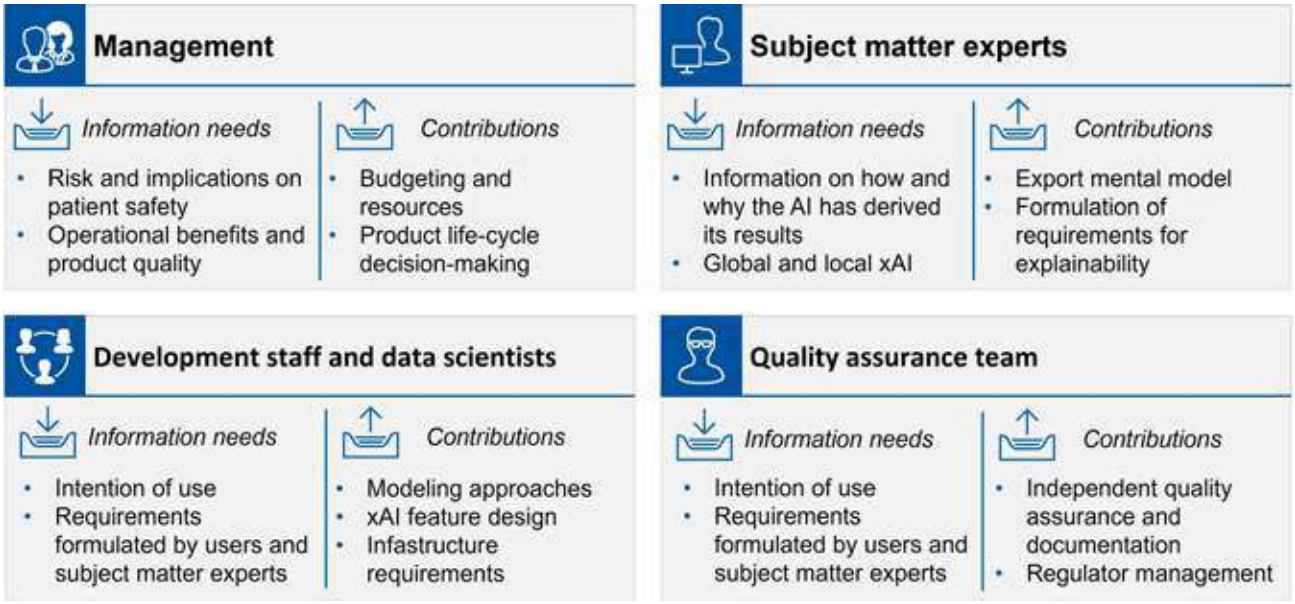
Continuing our introductory example on the identification of erroneous states, we present two xAI methods in Figure 2, representing ex ante explainability on the level of input data and ex post on the level of the model [9]. The input image can be a) processed by means of a a feature extraction method (Hough Transformation, a robust method to identify shapes like circles and lines) and b) compared to heatmaps that illustrate the class activation of neural networks in classifying an erroneous state. These could then guide the human operators in their decision, and could be used in a retrospective QA exercise. Furthermore, these outputs can support communicating the functioning of the algorithm and how it is embedded in operational procedures in an audit situation.

NEEDS AND RESPONSIBILITIES FOR xAI ACROSS CORPORATE FUNCTIONS

Driving a product through its life cycle in the GxP-regulated environment involves many stakeholders, each with their specific needs and responsibilities in unlocking the black-box nature of AI solutions (see Figure 3):

- Management needs to make educated decisions on whether the risks involved in productive operation are outmatched by the operative and patient-centric benefits, balancing the business and the product quality perspectives. To this end, the AI solution's functioning and limits should be made transparent such that the actual decision to run the system in production can be made and further guidance for development can be issued. It is the project's responsibility—involving both the development as well as the QA side—to provide this information in the level of detail suitable for management stakeholders.
- Subject matter experts (SMEs) represent the functional design of the solution. As such, they provide a "mental model" of the underlying functional mechanisms of the use case. They also curate the training and validation data that is used to train the model. Usually, they represent the user or even coincide with the consumers of the AI application's services. Therefore, SMEs are one of the main addressees of the solution's explainability features where we differentiated two needs:
  - Explainability on the model level (global understanding): SMEs need information on the model's overall behavior to match their mental model.
  - Explainability on the data-point level (local understanding):

Figure 3: Summary of needs and contributions of stakeholders regarding explainability for AI.



In the Human-AI-Team, explainability on the data-point level enables the user to understand how the solution has come to its conclusion. Depending on the intention of use, this may be directly necessary in a situation where the ultimate decision remains with the users. In such a situation, the users would augment their expert knowledge to the AI's result leveraging both strengths of the Human-AI-Team: Critical thinking and subject matter expertise as well as the capability to analyze large amounts of data. Furthermore, in automatic operating use cases, explainability on a single level is important to analyze sample or incident cases to understand potential areas of improvement. It is the SME's responsibility to formulate clear expectations on the explainability capabilities as part of the intention of use and model design.

- Development staff and data scientists must fulfill the explainability requirements by suitable choices of technology and presentation that support the needs of the xAI's audience. The same time, they may also gain a better understanding of the model to iterate to an optimal model choice. Decisions must be made on various levels:
  - Solution's modeling approach: When selecting AI modeling strategies, some models may be more open to explainability than others, typically at the cost of predictive power. Typically, regression- and tree-based models are much easier to understand than complex, deep-layered neural network approaches. These decisions should carefully reflect the needs to find an optimal compromise among various AI quality dimensions [7].
  - Explainability feature design: To fulfill the specific needs of the xAI's audience, explainability features must be integrated into the solution so that the target audience can build on this presentation. The challenges in this regard range from suitable algorithmic strategies, potential performance optimization, and suitable representation of results.
  - Infrastructure and computation power: xAI is generally resource-intense and has implications on the infrastructure required to support productive operation. In performing their task, the development team should keep an attitude of critical thinking: As more knowledge is accumulated during the development, explainability requirements may shift, offering even better approaches. Hence, continuous exchange with SMEs should ensure both that actual needs are met and learnings are quickly fed into the design process.
- QA team: The QA team is the other main addressee for explainability, so the team must evaluate whether the solution is fit for production as per requirements and quality expectations. This involves careful planning to measure the effectiveness of xAI. Typical approaches involve structured feedback on the analysis of example cases by SMEs, while the QA team must take care in designing the exercise in a way that a sufficient range of cases both in usual operation and edge cases are covered. In addition, the QA team must summarize the quality indications to management for decision-making processes. In addition, the QA function is in charge of demonstrating the control framework against auditors, where xAI will support the understanding and trust.

THE ROAD TO EXPLAINABLE AI ON THE PRODUCT LIFE CYCLE

The complex needs and responsibilities regarding explainability of an AI solution need to be structured in a framework to ensure

Table 1: Roadmap to explainable AI, orchestrating stakeholders' activities along the product life cycle.

Business Function/ Development Step	Management	Subject Matter Experts	Development Staff and Data Scientists	Quality Assurance Team
Intention of use design	High-level guidance on the solution's goal	Learning target specification User specification Data source specification Explainability expectation specification	Suggestions from technologically point of view Explainability expectation feasibility assessment	Insights from similar projects Regulatory requirements
Risk assessment	Guidance on acceptable risks	Explainability feature-driven risks: misguidance, target group adequateness, lacking level of detail, performance	Data feasibility, quality, and robustness	Support in deriving quality expectations on explainability features Guidance on the application of regulatory requirements to the intention of use
Model and explainability feature design		Clarification Feedback loop and explainability expectation refinement	Model and explainability means selection Prototypes and technical studies Critical feedback	
Model and explainability feature implementation		Feedback on usability	AI solution implementation and fine-tuning UI/UX design	QA planning (strategy and documentation definition)
Initial QA assessment and quality gate		Expert assessment		QA execution (testing, documentation, and reporting)
Productive operation and QA periodic review	Life cycle decision-making	Feedback on solution quality	Development planning	QA periodic review

that all required steps are performed along the development process. In the following overview, we propose a roadmap to orchestrate the stakeholders' activities, supporting the effective use of AI in GxP-relevant processes (see Table 1).

Intention of Use Design

Explainability must be considered from initiation of the project. The guiding question is: Who shall act in which situation based on the results of the AI solution? In answering this question, the basis for the following steps regarding explainability design is set:

- Who (the addressee): Identifying the addressee, i.e., the user or stakeholder to whom the AI's results should be explained. This may range from operators controlling the actual production process to subject matter experts and QA for validation purposes. It is crucial to understand the background and knowledge of the respective audience to provide the right level of detail for performing their tasks when interacting with the AI.
- Act (the action to be performed): Leveraging the AI maturity model [6], the target operating mode for the AI solution may range from full oversight to exception handling only. Understanding what the addressee must do is paramount to designing the optimal means of providing the required information; also, non-functional restrictions such as processing times must be considered.
- In which situation (the circumstances in which the explainability

features must achieve their effect): Circumstances may range from an office situation to the actual production environment with its impacts on space, sight, heat, etc. A good understanding of the situation in which the addressee use xAI is required to design appropriate technical means.
- Based on the results of the AI solution: This part of the question reflects the output of the AI. The form and delivery of an explanation depends highly on the input and output structure.

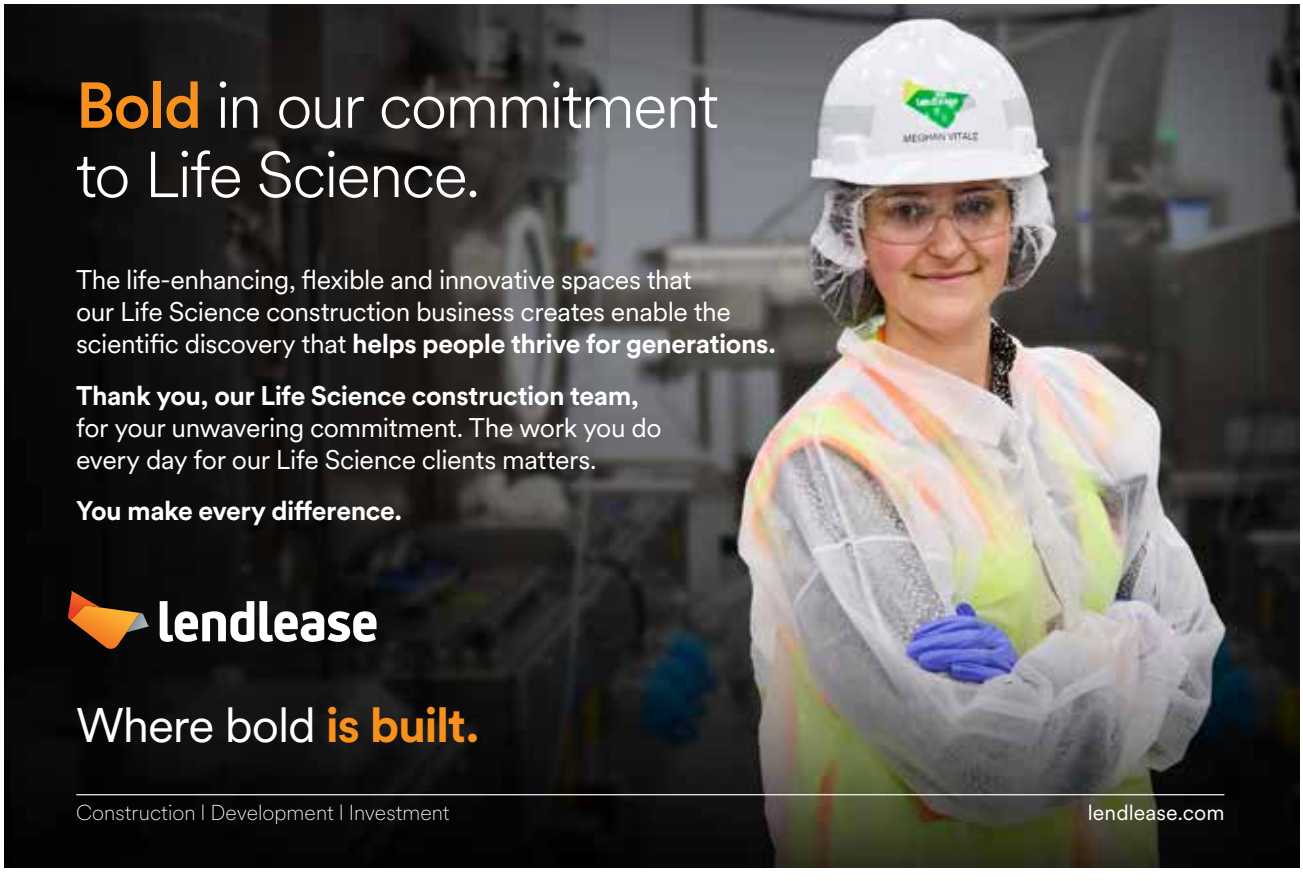
In this early stage, all parties can contribute to the target operating model, either from the functional side (formulating expectations and requirements) or from the technological side (showcase possibilities that might be unthinkable from a SME's point of view).

Risk Assessment

GxP is about ensuring an acceptable balance of risks to patient safety and their benefits. In that sense, explainability is one means to bridge the gap between what can be drawn from the data and what needs to be assessed by humans' intelligence. However, it is a mistake to generally consider explainability as risk mitigation strategy, as xAI carries risks on its own:

- Misguidance and target group inadequateness: Even though explainability is designed to support the user in drawing the right conclusions from the AI solution's output, xAI may suffer from the solutions' limitations and inadequate quality of the data used. Furthermore, the output may be misinterpreted by the audience.
- Mismatch between the data used for the model result and the data used for explainability features: It is crucial that the same data and state of model is used to determine the actual model result and it's explainability output presented to users. This could be provided by noting a checksum or a cryptographic proof on the data used, as well as strict tracing of the model versions.
- Lacking level of detail: Explainability cannot reveal the full mechanics of the model, which would be as complex as the model itself. Therefore, a decision on the level of abstraction must be made that determines the provided information. Whether this level of detail is sufficient should be carefully evaluated. Also, alternative means to perform the operators' action should be provided for unforeseen cases.
- Performance: The xAI may be too slow to be operational in the context of the system, as additional functionality renders a higher burden on the infrastructure in which the solution is running. This aspect should be carefully evaluated in infrastructure planning.

By means of a risk-based approach, management must decide which risks are deemed bearable compared to the benefits to be



During productive operation, data should be collected that allows the tracing of the AI solutions and its xAI.

expected from the use of AI, and where further investment is needed to reduce risks to an acceptable level. This should be codified by quality expectations that the AI solution including its explainability features have to fulfill to be considered safe for productive use.

Model and Explainability Feature Design

Once the intention of use, the addressees, and the acceptable risks have been identified, the solution should be designed in a way that it is able to fulfill its specific quality expectations. The impact of the steps on the modeling decision that precede this cannot be underestimated: When users are confronted with the solution's results in every single case to build their decision on the AI output, a different modeling strategy may be pursued from a situation where the solution operates in a mode when only exceptions are handled by operators.

However, it is important to critically reflect the decisions made so far, as more understanding of the use case will be gained once the first models are evaluated. Prototyping strategies for early feedback and alignment reduce the acceptance risks further down the development process stream. In this process, documentation regarding the decisions made is important to justify the model and explainability mechanism selection in an audit context.

Model and Explainability Feature Implementation

xAI must adhere to the same software engineering standards as the AI solution itself and the more classical computerized systems with which the solution is integrated. This means that code quality standards, automated testing strategies, and qualification must be maintained, based on the intention of use, the risk assessment and requirements that have been identified in the first two steps.

Training, alignment, and refinement should be planned to reach the quality expectations, especially since the addressees of explainability features may be inexperienced with those mechanisms.

As the target solution including explainability features becomes clear, the QA team should plan on how to validate the effectiveness of these mechanics during validation planning.

Initial QA Assessment and Quality Gate

As for other aspects of the solution, the goal of QA is to generate evidence on whether quality expectations are met. Earlier in the article, we suggested the concept of five AI quality dimensions that provide a blueprint to structure these expectations in an AI context. Here, explainability is one crucial part of the "Use Test" dimension, i.e., the acceptance of the solution by its users.

The following aspects are important to generate sufficient evidence that quality expectations are met:

- As a quality gate to productive operation, the QA assessment must cover an appropriate range of use cases and collect users' or SMEs' feedback on implemented explainability features.
- It is important to cover a suitable range of input and output scenarios: For instance, in binary classifications, explainability should work both for positive as well as negative cases along suitable stratifications of the input data space.
- The range of users is important to consider, starting with the new joiner scenario to experienced staff. This variety helps in aggregating insights on the overall effectiveness of the xAI.

The QA team should draw a holistic conclusion based on generated evidence and prepare the product life-cycle decision making by higher level management by means of weaknesses identified in the Human-AI-Team with an indication, jointly with the SMEs, on the criticality and potential for risks to materialize as well as further suggestions for improvement of the solution and its explainability features, e.g., regarding presentation of results, extensions of existing functionality, or changes in limitations applied to productive operation.

As for other validation exercises, documentation of the QA exercise requires a traceable path starting with the requirements for intention of use, along the risk assessment to the functional design decisions and the tested evidence, including the data used for tests and validation. For the specific aspects of xAI, we deem the assertions of users in how far the xAI supported in matching their mental model with the AI's results to be most important.

Productive Operation and Ongoing QA

During productive operation, data should be collected that allows the tracing of the AI solutions and its xAI:

- Input and output data: The version of the model, the input data known to that point in time, and the model results as well as the presentation to the user should be collected in a way to reproduce the situation for an ex-post investigation.
- If suitable in the use case, annotations by users to further qualify and show their interaction with the AI results should be kept. This should include both means of structured as well as free text input as well as images.
- Incidents in the context of explainability can be defined as cases in which the solution fails to provide suitable information to the user on how it reached its conclusion. In a GxP environment, a formal deviation management must be defined; i.e., it must be predefined under which circumstances a deviation record will be triggered. Furthermore, to allow for a targeted improvement of the AI and xAI tandem, the following cases should be considered:

- The AI solution's result is acceptable, although the xAI fails to communicate this result: This is an incident attributable to the xAI and offers opportunities to improve on the presentation of the model's result. Such an incident may stem from insufficient level or choice of detail or actual errors in the presentation. In particular, the former can be best understood in collaboration with users and their refined view on expectations of xAI presentation.
- The AI solution's result is not acceptable, although the explainability feature provides suitable insights on why the AI has come to its conclusion: This can be seen as an incident attributable to the AI model and offers opportunities to improve the predictive power of the solution. A follow up would be to investigate the model mechanics in more depth given the input.
- The AI solution's result is not acceptable, and the explainability features fail to communicate the result to the user: This incident should be attributed both to the AI model and to xAI and form the most critical part from an operational point as this hinders trust in the AI. Such cases should be thoroughly investigated and matched against the risk assessment's acceptance of such failures.

In the statistical setting of applying AI, raising awareness of the limitations and maintaining critical thinking are still required to augment artificial intelligence as needed by cognitive intelligence: If the user keeps the AI's limitations in mind and is provided with appropriate means to take over control, he can more easily trust the AI. Only based on this trust can constructive collaboration emerge.

This data will provide valuable insights on how to direct the solution through its life cycle, either from a product development point of view or as per corrective and preventive actions (CAPA) management. With regard to explainability, user feedback is the most important source to improve on the interaction with the AI. This should be classified by severity and qualified by observations or images to allow for an in-depth investigation.

GUIDANCE TO MEASURE xAI EFFECTIVENESS

The goal of xAI is to communicate the model's results to the SMEs. The evaluation of its effectiveness should cover the following aspects [10]:

- Acceptance of the results: In many use cases, users are still in control of the ultimate decision, or can judge on cases in an ex-post manner for a representative sample for QA purposes. Here, acceptance of the results can be measured by means of "overrides," i.e., cases in which the user opted for a different outcome than the algorithm. Based on this measure, the solution could be provided

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with or without xAI. Comparing these results, we can measure the effectiveness of the explainability feature.

- Efficiency: In many use cases, the xAI should support the joint decision-making of the Human-AI-Team. Hence, a performance benchmark can be drawn by comparison of average times to decision (each with a representative set of cases) if feasible: by classical means without an AI-featured solution; with the support of an AI-featured solution, but without explainability features; and with the support of an AI-featured solution and its explainability features in addition. We should expect that operating times decrease with the level of technology applied. In a sense, the time differences between with and without explainability features are the benefits of investment into an additional layer of technology to explain the AI's results. Surveys may catch qualitative input on the capabilities and limitations of the explainability features (e.g., general presentation, level of detail, overall trust in the solution).

CONCLUSION

The Human-AI-Team [5] can only work effectively by means of clear communication and understanding. Staff can draw the right conclusions, gain trust in the results, and take over control in case of statistical failures. The key to understanding AI is another layer of functional instruments: xAI. However, designing xAI will require compromises based on the intention of use and the risk assessment, considering the target audience of various business functions.

This takes AI one step further: Like humans providing an expert-based prediction along a narrative, xAI does so based on the input data and sharing insights into its model mechanics. With our roadmap to explainable AI at GxP, we show how to operationalize the analysis and decision making to arrive at a suitable setup tailored to the intention of use, with quality assured and therefore fit for production. Hence, the design process of xAI should begin at the very start of AI projects.

Continuous measurement of the effectiveness of the explainability features, as for every crucial gear in a GxP-governed process, ensures long-term usability and trust. Technological approaches have provided the capabilities to unbox the black-box nature of AI solutions. The next step is to integrate these instruments into the development and QA processes as another building block to grasp the potential of AI in life sciences.

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About the authors

Elias Altrabsheh started his career as a model developer working on health economics models in multiple therapeutic areas such as diabetes and infectious diseases. Since then, he has evaluated digital health therapeutic and technical projects concerned with developing machine learning/analytics/software as a service platforms in the healthcare space. At d-fine as Consultant, he applies his technical expertise to projects involving modeling and software development and is active within the pharmaceutical/health care community. Elias obtained an MSc in complex systems modeling at King's College London.

Martin Heitmann, FRM, jointed d-fine after completing his MSc studies in business mathematics at the University of Mannheim. His first projects were in the financial industry, where he designed large data pools to apply predictive analytics for rating assessments. As d-fine expanded its operations to other industries, Martin took part in the formation of the pharmaceutical and health care unit. As a Manager, he transfers process design, data science, and large-scale implementation expertise to post-market surveillance under the medical device regulation, the implementation of a prescription settlement platform, and digitalization projects for senior residence operators. In the collaborative pharmaceutical community, Martin is an active member in various knowledge-sharing platforms.

Patrick Steinmüller graduated from the University of Cambridge with an M.a.St. in Mathematics (Tripos Part III), and joined d-fine in 2016. He is a Manager with responsibilities for applied artificial intelligence (AI), explainable AI, and quantum machine learning. d-fine is part of PlanQK, an incubator for applied quantum computing technologies, extending feature-attributive xAI methods to variational quantum circuits.

Bruna Pastori Vinco is Validation and IT Quality Assurance Manager at Fresenius Kabi Deutschland GmbH. She holds a degree in pharmacy and an MBA in project management. With more than 10 years of experience in the GxP-regulated industries, Bruna is an expert on computerized systems validation and data integrity. As a member of the ISPE GAMP® D/A/CH's working group for artificial intelligence (AI) in GxP areas, she contributes to initiatives to establish guidelines and best practice approaches for the validation of AI and machine learning applications. She has been an ISPE member since 2016.

WHAT YOU NEED TO KNOW ABOUT *GAMP® 5 Guide, 2nd Edition*

By Siôn Wyn and Chris Clark, BSc

ISPE's *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems (Second Edition)* (*GAMP® 5 Guide, 2nd Edition*) maintains the principles and framework of the first edition and updates their application in the modern world, including the increased importance of service providers, evolving approaches to software development, and expanded use of software tools and automation. The 2nd Edition highlights the use of critical thinking by knowledgeable and experienced subject matter experts (SMEs) to define appropriate approaches.

Since the publication of the first edition, *GAMP® 5* has been far and away the leading international guidance on GxP computerized systems validation and compliance. It was time for ISPE to update this key guidance document to reflect technological progress.

GAMP® 5 Guide, 2nd Edition, aims to continue to protect patient safety, product quality, and data integrity by facilitating and encouraging the achievement of computerized systems that are effective, reliable, and of high quality.

The overall approach, framework, and key concepts remain unchanged from the first edition. The technical content of the guide has been updated to reflect the increased importance of information technology (IT) service providers including cloud service providers, evolving approaches to software development including incremental and iterative models and methods, and increased use of software tools and automation.

Guidance on the application of new and developing technological areas such as artificial intelligence and machine learning (AI/ML), blockchain, cloud computing, and open-source software (OSS) has been included or updated. The importance of critical thinking and the application of patient-centric, risk-based approaches (aimed at quality and safety) versus primarily compliance-driven approaches is further underlined. Concepts of computerized software assurance (CSA) as discussed in the US FDA Center for Devices and Radiological Health (CDRH) Case for Quality program [1] are also explored and applied.

BACKGROUND AND DRIVERS

One of the reasons GAMP guidance has always been successful is that it has always sought to accurately reflect current, good IT and software engineering practices, based on input from experienced IT, automation, and software practitioners. To be of optimal value to the industry, GAMP guidance must be well-aligned with current good practice. GAMP should not provide 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 the same way that it would be considered unacceptable by the public and the health authorities for regulated organizations to apply old-fashioned, superseded, and outdated medical science or medical practices, it would be unacceptable for such organizations to apply outdated IT and software practices, as this would be inefficient, ineffective, and ultimately extremely detrimental to public health.

As clearly stated by the US Food and Drug Administration (FDA) [2]:

"The CGMP requirements were established to be flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures. The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Accordingly, the 'C' in CGMP stands for 'current,' requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment that may

have been 'top-of-the-line' to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards.

"It is important to note that CGMPs are minimum requirements. Many pharmaceutical manufacturers are already implementing comprehensive, modern quality systems and risk management approaches that exceed these minimum standards."

In the same way, we also need to apply software development methods and techniques that are adequate by today's standards. However, too many examples of ineffective and inefficient practices remain for reasons including organizational inertia, lack of experience and training, a shortage of effective business process and technical SMEs, overreliance on compliance-driven tick-box approaches, and a misguided fear of perceived regulatory inflexibility.

FRAMEWORK AND OVERALL APPROACH

GAMP® 5 Guide, 2nd Edition, prioritizes patient safety and product quality over compliance and encourages the application of critical thinking. The 2nd Edition strongly supports the FDA Center for Drug Evaluation and Research (CDER) vision of a maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight, where the vision requires moving beyond simply meeting minimum CGMP standards and toward robust quality management systems [3].

The overall GAMP 5 framework, key concepts, and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q9 aligned quality risk management (QRM) approach remain unchanged from the first edition. The technical content of the guide has been updated to reflect the increased importance of IT service providers including cloud service providers, evolving approaches to software development including incremental and iterative models and methods, and increased use of software tools and automation. The 2nd Edition builds on the work of the ISPE *GAMP® Good Practice Guide: Enabling Innovation* [4].

The 2nd Edition further emphasizes that the GAMP® life cycle, specification, and verification approach is not inherently linear, and that it also fully supports iterative and incremental (Agile) methods. The guide describes how critical thinking should be applied through the system life cycle, explaining how the life cycle phases apply in Agile situations as well as linear, and encourages the maintenance of records and information in appropriate and effective software tools. The increased use of cloud-based applications is also reflected. As part of the ICH Q9 aligned QRM approach, new guidance on process risk assessment has been added.

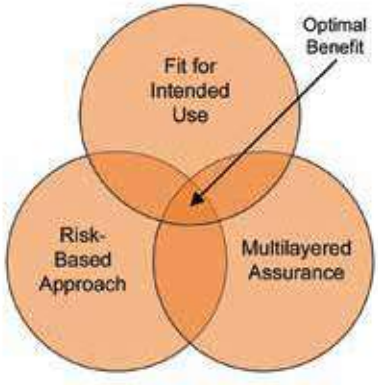
UPDATED AND NEW APPENDICES

Guidance on the application of new and developing technological areas such as AI/ML and blockchain has been included. The concepts of CSA related to US FDA CDRH Case for Quality program are also explored and applied where relevant.

Figure 1: Iterative and incremental approach to achieving compliance and fitness for intended use. (Source: *GAMP® 5 Guide, 2nd Edition* ©2022 ISPE, all rights reserved.)



Figure 2: Critical thinking for computerized systems. (Source: *GAMP® 5 Guide, 2nd Edition* ©2022 ISPE, all rights reserved.)



Management Appendices

Highlights of updates and new material in the management appendices include:

- Addressing the validation planning and reporting of software as a service (SaaS) solutions and systems developed or configured in an incremental or iterative manner (Agile)
- Addressing assessment of cloud service providers, and the use of cloud platforms and applications, which move some risk management activities outside the regulated company
- Categories updated to reflect that:
  - Computerized systems are generally made up of a combination of components from different categories, and that categories 3-5 should be viewed as a continuum
  - The software category is just one factor in a risk-based approach; the life-cycle activities should be scaled based on the overall

GxP impact, complexity, and novelty of the system (derived from the criticality of the business process supported by the system) and the nature of the components and technology involved

- Encouraging automated and tool-based reviews and verification, and automated traceability rather than manual traceability approaches
- Discussing Agile toolsets to manage requirement changes, artifacts/deliverables, and for DevOps and continuous integration/deployment
- Reflecting evolving approaches to information management, moving from traditional paper formats to searchable tool-based information life cycles. Acknowledging implicit as well as explicit knowledge
- Reemphasizing that records and information are maintained because they are valuable to the regulated company as their source of truth, and not necessarily for demonstrating to a third party
- New appendix applying current risk-based thinking on good practice for managing infrastructure that resides within a regulated company's own facilities as well as those of external suppliers, such as cloud-based suppliers of infrastructure as a service (IaaS), platform as a service (PaaS), and SaaS
- New appendix discussing the application of critical thinking to proactively optimize the approach taken to ensure quality and compliance of computerized systems (through better specification, development, testing, operation, and maintenance) within the context of the business processes they support.

Development Appendices

Highlights of updates and new material in the development appendices include:

- Updated guidance on requirement and specifications, taking into account Agile development methods and the increased use of tools and automation in the capture and definition of requirements
- Testing guidance updated to emphasize that:
  - Critical thinking should be applied when planning testing efforts: the regulated company should determine the type and level of assurance activities required, based on their own need to ensure systems are fit for intended use, commensurate to the risk acceptable within the organization as defined in its policies, procedures, and plans
  - Testing by any means and in any part of the life cycle and in any environment (development, validation, production, DevOps, etc.) all contributes to finding defects and confirming the system is fit for intended use
  - Testing should not be limited to detailed and prescriptive step-by-step scripted protocols—the use of exploratory testing and other unscripted techniques is encouraged to extend test coverage and improve defect detection



- Using automated testing brings benefits to test coverage, repeatability, and speed
- Modern approaches may rely on records, information, and artifacts in automated tools in place of formal specification and test documentation

- New appendix provides a summary of the principles underpinning Agile and illustrates how it can be implemented in a way that is aligned with GAMP® 5 and GxP principles; the focus is on how to use well-implemented standard Agile processes to deliver software for GxP applications and does not advocate modifying Agile for GxP, for example, by superimposing duplicate and unnecessary linear ("V-model") activities
- New appendix describing the recommended risk-based approach and considerations when using tools supporting computerized systems life-cycle processes, IT processes, and IT infrastructure processes; such tools do not directly support GxP-regulated business processes or maintain GxP records and data directly supporting the regulated product life cycle
- New appendix on blockchain aiming to assist in ensuring that the usage of computerized systems applying this technology does not introduce new risks to patient safety, product quality, and data integrity
- New appendix on AI/ML, providing a basic understanding of these technologies, and guidance on how to ensure compliance integration and fitness for use in a GxP environment

Operation Appendices

Highlights of updates and new material in the operation appendices include:

- Updated process flow and expanded definition of handover activities, recognizes use of support tools, and including discussion of hypercare and business readiness
- Expanded consideration of service-level agreements (SLAs), which recognizes other aligned agreements such as quality agreements; includes consideration of contract exit
- Addressing the use of modern monitoring technologies
- Further clarification of the relationship between incident management, problem management, and deviation management
- Highlighting the use of IT service management tools in incident and problem management
- Enhanced description of relationship between regulated company, IT, and external service provider's change processes
- Utilizing metrics and trends to determine fitness for intended use
- Clarification of business continuity and disaster recovery processes and their relationship, and establishing a link to incident and problem management; include considerations for anything as a service (XaaS)
- Include considerations of current data IT security practices aligned with industry standards such as ISO 27001 and National Institute of Standards and Technology (NIST)

Special Interest Appendices

Highlights of updates and new material in the Special Interest Appendices include:

- Consideration of cloud computing technologies and blockchain technology included for electronic production records (EPR)
- Additional material on real-time generation of reports for review by exception (RBE) and other functionality from EPR
- Clarification on data audit trails and data audit trail review for manufacturing systems
- Additional data integrity considerations for end-user applications including spreadsheets and more detailed risk-based decision recommendations

CONCLUSION

GAMP® 5 Guide, 2nd Edition, seeks to meet and exceed minimum compliance expectations by encouraging the application of modern, current, good IT practices; robust QRM approaches; and excellence in software engineering to achieve better product quality and safety for the benefit of the patient and the public.

For more information, visit the ISPE Guidance Document site: https://ispe.org/publications/guidance-documents/GAMP®-5-guide-2nd-edition

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About the authors

Siôn Wyn, Director, Conformity Ltd., is an acknowledged expert in computer system validation and compliance, data integrity, electronic records and signatures, and international regulations in this field. Siôn assisted the FDA as a consultant with its reexamination of 21 CFR Part 11 and was a member of the core team that produced the FDA Guidance on 21 CFR Part 11 Scope and Application. He received the FDA Group Recognition Award for work on Part 11. Wyn is co-lead of ISPE's *GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems, 2nd Edition*, was Co-Lead of the ISPE *GAMP® Guide: Records and Data Integrity*, and is a member of the ISPE GAMP Global Steering Committee, GAMP Editorial Board, and the GAMP Europe Steering Committee. Siôn received the 2006 ISPE Professional Achievement Award and the ISPE UK Fellow Award in 2016. He joined ISPE in 1995 and is Technical Consultant to ISPE.

Chris Clark, BSc, is Director of TenTenTen Consulting Limited, providing advice and support to overcome the business and regulatory challenges to patient safety, product quality, and data integrity. With over 40 years of experience with QCIQA covering various GxP pharmaceutical fields, he has specialized experience in ensuring compliance of a wide range of computerized systems (laboratory and clinical systems, MRP systems, and documentation management systems). As Chair of the GAMP Editorial Board and a member of the ISPE GAMP Global Steering Committee and GAMP Europe Steering Committee, he has contributed to the publication of several GAMP guidance documents, most notably ISPE's *GAMP® 5 Guide: A Risk-Based Approach to Compliant GxP Computerized Systems*. Additionally, Chris is a member of the ISPE Guidance Documents Committee. He has been an ISPE member since 1997.

USING TECHNOLOGY
for Continuous Process Verification 4.0

By Marc Olivé Torralba, Bryon Hayes, PEng, and Marc Ramoneda Rueda

In this article, potential Pharma 4.0™ technological solutions that can enhance continuous process verification (CPV) 4.0 are discussed. The necessary paradigm shift will allow companies to predict deviations more accurately, perform root cause analysis (RCA), ensure data integrity and GxP compliance, and ultimately be more competitive in a highly regulated industry.

This article is the second part of the "Reimagining CPV for a Pharma 4.0™ World" article published in the May–June 2022 issue of *Pharmaceutical Engineering*® [1]. In that article, the business requirements were analyzed. The goal of this article is to showcase potential technological solutions that can enhance CPV for a CPV 4.0 by matching already available Pharma 4.0™ technologies with specific business requirements. This article is based on the defined framework and the implementation approach described herein.

CPV 4.0 VALUE PROPOSITION

The end goal of a CPV implementation is to ensure process robustness through the adequate and timely monitoring of processes. The best way to ensure robust processes is by predicting potential deviations that could affect batch performance. Applying Pharma 4.0™ technologies to CPV programs will enable this vision for predictive monitoring by making it technically feasible to:

- Predict deviations more accurately with artificial intelligence (AI)/machine learning (ML) algorithms
- Perform RCA from a holistic viewpoint
- Ensure data integrity and GxP compliance in predictions and RCA

Thinking further, CPV 4.0 offers a compelling dual advantage: It can predict deviations in real time and it can eliminate lengthy and costly back-end quality control testing upon batch completion. Both advantages lead toward real-time release.

FROM A USER-CENTRIC TO A DATA-CENTRIC MODEL

The foundations of a CPV 4.0 program lie in the data in the true "big data" sense (high volume, variety, validity, and velocity). CPV 4.0 requires a paradigm shift in the pharmaceutical industry. The current manufacturing scenario is built on a user-centric data consumption schema, where the users establish which data are needed for their jobs, and then the information technology (IT) and quality assurance (QA) departments make the necessary system modifications to get that data in the right structure, context, and level of certification.

This ad hoc strategy is rigid, expensive, and slow. For example, based on benchmarking different cases, inserting four additional data points as tags into an existing data store would require an

Figure 1: A summarized flow chart of a query life cycle with the user-centric model approach.

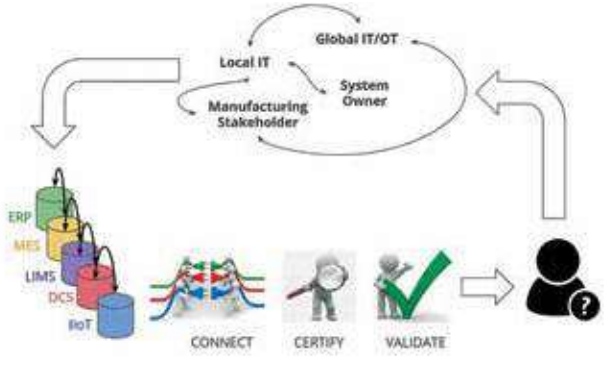
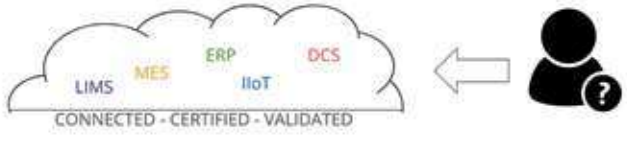


Figure 2: A conceptual view of a query life cycle using the data-centric model approach.



The most challenging steps in developing a CPV 4.0 technical solution are related to the data workflow: data acquisition, data contextualization, data modeling, and data visualization.

entire week of IT and QA collaboration. Costs include the direct full-time employee costs of making the change and the opportunity costs of IT and QA resources. This slow and rigid strategy runs counter to the flexibility and efficiency required in a constantly changing environment.

Figure 1 illustrates the query life cycle of a user-centric model where all the previously mentioned strategies were applied, making each query more costly and slower.

New manufacturing trends indicate that the proper data gathering and access scenario should be based on the manufacturing intelligence ontology (MIO), where the actors and their interactions are both considered.

The MIO leads to a data-centric model, where users access data from a regulated data hub and where all proper data contextualization and certifications only have to be performed once. In that case, the user has direct access to the qualified data, which is more efficient and faster because all the data silos are broken down, as shown in Figure 2.

KEY ELEMENTS OF A DATA-CENTRIC MODEL

Cloud Infrastructure

A cloud-hosted data store is ideal for the large volume of heterogeneous data required for a CPV 4.0 approach. Data from disparate sources (i.e., process, environment, human resources, maintenance) are automatically collected and transmitted to the cloud, reducing the inherent compliance concerns regarding manual data collection. This has the dual effect of breaking down data silos and enhancing data integrity.

The cloud offers many benefits and risks to a regulated organization. Interoperability and flexibility are paramount with the cloud. Scalability is a key benefit. CPV 4.0 needs a lot of computation power for ML model training and predictive analysis. The cloud offers an elastic resourcing paradigm for storage, computing, and networking resources. Fault tolerance is inherent in a cloud environment, as the operational resources are decoupled from the physical world of servers, switches, and storage. A major risk for regulated organizations is the loss of direct control over their data. If proper controls are not put into place, data security and data integrity may be compromised.

There are many models for cloud deployment, but the virtual private cloud model is most amenable to regulated organizations. A virtual private cloud is a private cloud run on shared infrastructure. It allows for the company's cloud resources to be isolated from that of other individuals or organizations. This encapsulation increases data security and privacy and reduces risk.

One consideration when using the cloud is the financial impact on an organization. The total cost of ownership (TCO) of IT infrastructure is difficult to ascertain as the mode of procurement shifts from a traditional capital expenditure (CAPEX) model to a subscription-based operating expenses (OPEX) model. The elastic nature of resource allocation in the cloud means that the cost will vary. An increase in computing power requirements for AI model training brings a higher price tag, so careful planning is necessary to avoid surprises. The cloud allows for a reduction in IT maintenance costs, as the subject matter experts from the cloud service provider are leveraged to ensure the security, reliability, and availability of the cloud. The elimination of CAPEX costs in the cloud can lead to a TCO that is one-third that of traditional IT infrastructure [2].

It is becoming more common for larger cloud service providers to add ALCOA+ (Attributable, Legible, Contemporaneous, Original, Accurate + Complete, Consistent, Enduring, Available) considerations to their offerings, making it easier for a regulated company to perform GxP activities in the cloud. The regulated company is responsible for including its use of the cloud in its quality management system (QMS) and other quality documentation. QMS considerations include:

- The means of creating and managing user accounts for administering cloud services
- Training appropriate personnel to perform their job functions in the cloud
- Internal auditors being familiar with the cloud and any auditing tools or resources available to help auditing within the cloud
- Performing supplier evaluations to establish the quality practices of a cloud service provider

It is important to build quality concepts into a service level agreement and to have a supplier quality agreement that addresses the concepts of reliability, availability, data security, privacy, change management, disaster recovery, communication and reporting of issues, and data access [3]. Data regionality may also be a concern in some applications. Ultimately, responsibility for and ownership of the data remain with the regulated company regardless of where data are stored, so the company must be vigilant when leveraging the cloud for a CPV solution.

Data Contextualization

Organizing data in a meaningful manner has obvious advantages for the scalability of a solution. For example, if we are

capable of contextualizing information for a batch where a feature analysis is needed, multiple batches need to be extracted for this analysis, facilitating the whole process. Furthermore, when we have similar processes, there is value in having similar data structures that can help scale the data analysis faster. For example, for a group of process units such as reactors or freeze driers that run very similar processes, the data structures could be set up in a similar manner.

When referring to an industrial process, we often describe data context as having two main components: asset context and batch event context.

Asset context

In asset context, we organize information with the physical representation of our factory assets as a baseline. Very often this is described as an asset digital twin, a collection of which may support and be components parts to the digital twin of a factory.

As an example, we could take any asset inside a factory that participates in a process and associate all the data belonging to it. This will provide a good representation of the variables that can be monitored inside this process.

When creating an asset context, it is relevant to decide between different possible standards. A hierarchical representation with different levels will facilitate this contextual organization, but it will require an alignment with the content/concept associated to each level.

Batch event context

Batch event context is especially important when trying to categorize data. It is important to have not only a digital twin representation of all the assets that participate in a manufacturing process (such as motors, rotors, reactors, and valves), but also a good process context of all the events. For example, if we want to retrieve data from a certain equipment unit belonging to a certain batch (or an operating procedure), it is imperative that this process digital twin is well identified. This is an important step before working on advanced modeling or AI techniques because our data will be much better prepared for analysis.

The ISA 88 batch standard [4], which provides a good guideline for creating an equipment/asset hierarchy as well as a process hierarchy (asset digital twin and process digital twin), could be helpful for categorizing data.

VALUE DRIVERS AND COMPLIANCE REQUIREMENTS

The most challenging steps in developing a CPV 4.0 technical solution are related to the data workflow: data acquisition, data contextualization, data modeling, and data visualization. Each of these steps has its own possible technical solution with unique compliance requirements.

Real-time data acquisition is key to breaking down the data silos and avoiding manual data handling. This approach will reduce time and effort, data integrity risk, and nonquality costs. Compliance requirements provide guidance on how data should be stored. Data must always be attributable, stored in a legible format, have timestamps for each life cycle step, be documented by a X.509 certificate granted in origin, and have build usage and metadata storage. In addition, the data location (regionality) and data storage (reliability) must be properly managed.

The technical requirement for data contextualization is to have scalable data models so that we do not have to start from scratch when adding new equipment and/or data sources. Compliance requirements exist for how data are normalized. Contextualization is done in the cloud with hot, warm, and cold access, and time synchronization and updates are under change control. A possible technical solution is creating context models in JavaScript Object Notation (JSON) format (the format of "big data"). JSON allows for the management of structured and unstructured data.

Data modeling (statistical or ML) allows predictions of and alerts for out-of-specification and out-of-trend data and can encourage operators to take proactive action to bring the process closer to the "golden batch" state. In this case, the technical need is to have flexible computational power (serverless cloud technology could help here) depending on the ML models to create, train, or execute.

In the end, data visualization is a real-time monitoring solution that enables proactive actions. Compliance requirements exist for how data are used. Usage must be logged and tracked, security and access rights must be controlled, data must be monitored for risk assessment, continuous backups are necessary, and data retirement must be managed.

THE CPV 4.0 ROADMAP

The vision of CPV 4.0 cannot be considered complete without a clear end state and a roadmap for how to get there, which is difficult to define given the status of the industry on CPV implementation.

One of the main roadblocks to evolve through a CPV 4.0 roadmap is that there is no AI model life cycle strategy for manufacturing, where an AI model is built, qualified, and validated into a specific process.

However, applying AI in a CPV context is achievable through a strategically developed algorithm qualification process. Discussions around AI algorithm qualification processes have already begun. Several papers have been published, but agencies, manufacturers, and suppliers are still looking for an official standard procedure to qualify AI algorithms, allowing their use in a regulated environment.

ISPE and GAMP are working in this area; for example, see *Pharmaceutical Engineering*, November–December 2019 [5]. ISPE also recently published the *GAMP® Good Practice Guide: Enabling Innovation* [6] that expands upon this discussion.

CONCLUSION

We are in the middle of a considerable challenge: a paradigm shift in a reputably risk-averse regulated industry to apply more innovative and cutting-edge technology to stay competitive.

In recent years, a few trends have emerged in the pharmaceutical industry: the evolution of treatments from blockbusters to personalized medicine; the pressure of being more competitive in a global market; and an industry in which the big companies seem to be more interested in mergers and acquisitions than developing their own pipelines. The need to change the paradigm is more urgent than ever.

As much as markets and companies evolve, technology is evolving even faster. Most ML algorithms were designed decades ago. It is only recently that the democratization of technology has allowed for the viability of implementing them.

Further, when technology is available and compliance aspects are addressed, the main roadblock for a CPV 4.0 rollout is the cultural mindset.

The Acatech Industrie 4.0 Maturity Index [7] emphasizes that the key to the successful implementation of any technology in a manufacturing organization is through the realignment of the company culture.

The focus should be on two specific principles: a willingness to change and the adoption of social collaboration. The emphasis on change essentially means that companies should focus on the value that can be derived from allowing mistakes, innovating, and pushing for decisions based on data and its analysis. Social collaboration means democratizing decision-making, encouraging open communication, and establishing confidence within the workforce in the processes and systems chosen to enable a digital transformation. The workforce, from management to workers on the manufacturing line, must be ready and willing to adopt to these changes.

These concepts translate directly to a CPV 4.0 approach, as regulated companies seek to employ technologies such as the cloud and AI/ML to improve processes. The chicken-and-egg cycle must be broken: processes are not being improved because there is not enough data (in quantity and quality), and ML/AI is not being used because it will require revalidation of the process.

Finally, the change management process is key to advancing through the Pharma 4.0™ paradigm shift. Creating centers of excellence and applying governance models would help to unblock situations within big organizations.

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About the authors

Marc Olivé Torralba is Data Solutions Director at the AG Solution Group. He has nine years of experience in digitalization projects for various industries, especially food and life sciences.

Bryon Hayes, PEng, is Director of Smart Manufacturing Solutions at Grantek Systems Integration Inc., where he manages a portfolio of products and solutions aimed at supporting the pharmaceutical industry. He has 20 years of experience executing and managing automation and information projects for pharmaceutical manufacturers. Bryon holds a bachelor's degree in systems design engineering from the University of Waterloo in Waterloo, Ontario, Canada. Bryon has been an active member of ISPE since 2009, and is a member of both the Pharma 4.0™ Special Interest Group and the Blockchain Special Interest Group.

Marc Ramoneda Rueda is Business Development Director for Europe at Klinea Biopharmaceutical Engineering, responsible for developing the BioPharma 4.0 vertical inside Klinea. He has a chemical engineering and international MBA background, and has worked in the biopharmaceutical manufacturing space for more than 20 years. His experience has included selling process equipment, engineering projects, automation and validation of turnkey biopharmaceutical projects, and most recently delivering a GxP artificial intelligence SaaS platform to optimize manufacturing processes. Marc has been an ISPE member since 2018.

2022 ISPE Europe Annual Conference Madrid: In-Person Again

By Thomas Zimmer, PhD

The ninth ISPE Europe Annual Conference was the first in-person conference after a break of over two years due to the pandemic. For travel-related reasons, some attendees participated remotely. With 450 participants on-site and nearly 490 total attendees, the usual atmosphere of an ISPE conference was present.

The keynotes addressed biologics—the fastest-growing sector of pharmaceutical drugs—and among those, cell and gene therapy approaches as well as personalized medicines. Biologics are a challenge for all functions in operations departments: from research and development to production, engineering, and IT to quality and supply chain excellence. Including cross-functional teams is a success factor for the future of biologics.

Representatives from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) discussed the role of regional regulatory agencies in addressing current challenges for the pharmaceutical industry and suppliers, and public health and safety. Top priority is given to avoid drug shortages; improve accessibility to vaccines; further innovation; and driving digital transformation, sustainability, and continuous improvement of quality and GXP compliance as the essential ground of patient safety.

ISPE's Facility of the Year (FOYA) category winners were presented, with their lighthouse projects to disclose the future. More detailed information about specific sessions follows.

AEMPS OVERVIEW

Maria Jesus Lamas Diaz, Chair of Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), the Spanish health authority, opened the Executive Forum with an overview of AEMPS' national and international activities, as well as Diaz's personal involvement in European committees. The initial impact of COVID-19 was supply chain disruptions, hindered production, and a sudden increase in demand.

From AEMPS' perspective, the ongoing supply chain needs are continuous monitoring of sales, existing stocks, and scheduled new batches. AEMPS also anticipates peaks in demand and control of supply for certain products. The continuity plan put forth by the regulatory authority has the following elements: (a) GXP inspections completed remotely as long-distance assessments due to travel restrictions; (b) the need to support marketing authorization and variations procedures, and to implement regulatory flexibility policy, agreed upon at the European Union (EU) level; (c) the need to tackle shortage problems; and (d) enhanced support for COVID-19 vaccine development (e.g., by providing GMP inspection resources).

DIGITAL TRANSFORMATION

Marco Odoardi, Senior Director, Head of Global Warehousing and Distribution for Merck KGA, continued the conference with a session focused on digital transformation of the pharmaceutical industry and the Pharma 4.0™ holistic approach within Merck Healthcare.

Digital transformation allows the pharma industry to shape the future and to gain and sustain competitiveness in time. "Digital transformation starts as a trickle…and builds to a flood," said Odoardi. It allows organizations to fully live up to their accountability and to operate with autonomy and command of the products. It goes hand in hand with the increasing digital maturity, being closer to the business to accelerate value creation, and being a competitive advantage to the company.

Odoardi discussed the structured Merck approach, which is built around three dimensions: Set the aspiration, deliver higher-priority use cases, and sustain it. "A particular emphasis will be placed on the culture and people involved," he said, noting that business drivers and logic are "sterile" if the required mindset and behaviors are not embedded in the organization.

Merck targets "where people are the success factor and will be game changers in the external environment on the successful digital transformation." There is no magic bullet for successful digital transformation, he said, and it won't happen overnight. But there are best practices and ways to create conditions for success. Fostering a digital-impact-driven culture and driving people development are key to ensure replicable success.

TECHNOLOGY TRENDS

Paul W. Rutten, Partner, McKinsey & Co., led a session entitled "Tech Trends that Matter." Advanced technology has always spurred economic development, and now it's accelerating even faster, he said. In the next decade, the world will experience more progress than in the past 100 years combined as technology reshapes health and material sciences, energy, transportation, and a wide range of other industries and domains. This progress will have broad implications for the industry.

Each industrial revolution was driven by advanced technology—the first by the steam engine (1769), the second by the internal combustion engine (1867), and the third by the internet (1970s). The fourth will be driven a range of scientific research streams collectively known as "omics," Rutten said. McKinsey plans to research technologies that will fuel the fourth industrial revolution as well as the impact from the upcoming bio revolution.

Omics include three main categories: intracellular flow of genetic information, intracellular products of metabolism, and others. The first, intracellular flow of genetic information, includes epigenomics, epigenomic DNA modifications, transcriptomics, and proteomics, which are described next:

- Epigenomics: The full genetic complement of an organism; relatively static over time.
- Epigenomic DNA modifications: Epigenetic marks that regulate gene expression (e.g., DNA methylation, histone protein modification).
- Transcriptomics: The complete set and quantity of RNA transcripts that are produced at a given time.
- Proteomics: The entire set of proteins of an organism with changes over time.

The second, intracellular products of metabolism, includes metabolomics, glycomics, and lipidomics, which are described next:

- Metabolomics: A set of metabolites, small molecule intermediates, and products of metabolism.
- Glycomics: The structure and function of the complete set of glycosylated products (e.g., glycans).
- Lipidomics: The complete set of lipids produced.

The third category describes other omics: microbiomics, single-cell omics, and circulating cell-free DNA or RNA analysis:

- Microbiomics–Microbe population: All microbes in a population (e.g., the human gut).
- Single-cell omics: Includes human and other cells and captures single-cell-level nuances that aggregation across multiple cells would miss.
- Circulating cell-free DNA or RNA analysis: DNA/RNA in bloodstream, not in cell; noninvasive or transcriptome information.

DIGITAL THERAPEUTICS

Giuseppe Recchia, CEO, daVinci Digital Therapeutics, addressed the barriers and challenges within digital therapeutics. One of the main issues in this sector is missing or incomplete definitions of terms. For example, digital health includes technologies, platforms, and systems that engage consumers for lifestyle, wellness, and health-related purposes to capture scores, transmit health data, and potentially support life science and clinical operations. However, programs within digital health do not require clinical evidence or regulatory oversight.

Digital medicine includes evidence-based software and hardware products that measure or intervene in the service of human health and that require clinical evidence and regulatory oversight. Digital therapeutics are medical devices considered a subset of digital medicine that deliver an independent therapeutic intervention and require clinical evidence or real-world outcomes. Regulatory oversight, not applied today, is needed.

Another barrier for digital medicine is the heterogeneous landscape of reimbursement within the various countries, with some more advanced than others. There is a complex landscape of disease management purposes that requires specific regulation approaches, such as well-being apps; remote monitoring; digital offerings for therapeutics and rehabilitation; and digital support for diagnosis, self-management education, and drugs.

Recchia closed with a future vision for the development of national digital health laws, stating that they will need to address the following topics: (a) doctors are allowed to prescribe medical apps; (b) improved access to patient data for research; (c) health care providers move patient communication and prescriptions to electronic channels; (d) every insured member has access to an electronic health record; (e) health insurers are allowed to offer online member signups; (f) health innovation is financially supported; (g) telehealth consultations become the norm; and (h) pharmacies, health care providers, and hospitals must connect to a secure communications network.

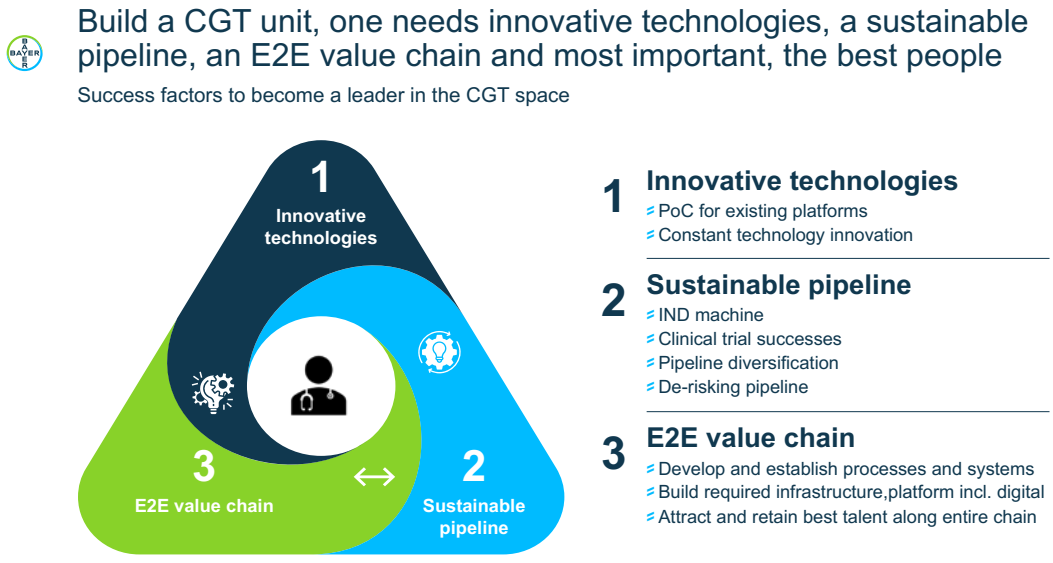
CYBERSECURITY

Enzo Tieghi, President, ServiTecno Srl, and Chair of the ISPE GAMP® Forum Italy, highlighted the need for cybersecurity. His main message was that cybersecurity is not only a matter of information technology, but also of operation technology because the digital transformation also changes the cybersecurity perspective in operations. Within information technology, cybersecurity is necessary to protect data and information. Within operation technology, cybersecurity is necessary to protect systems that manage the controlled process.

Surveys indicate that after the energy sector, the health sector is the second-most targeted for criminal actions. Manufacturing is also in the top five targets. Thiegi outlined key pharma security breaches to know and learn from.

- 2014—Dragonfly malware attack: This cyberattack on the pharma supply chain was one of the first high-profile cyberattacks on the pharma industry.
- 2017—NotPetya malware attack on Merck: This attack is considered one of the most expensive and devastating in history. It affected over 30,000 computers, caused over $870 million in damages, and resulted in $410 million in lost sales.

Figure 1: Success factors for building a cell and gene therapy unit (source: Bayer AG and Wolfram Carius).



- 2018–2019—Winnti malware attacks on Bayer and Roche: The purpose of these cyberattacks, thought to be linked to a state-backed Chinese hacking group, seemed to be industrial espionage.
- 2020—Dr. Reddy's Laboratories data breach: The Indian drugmaker was forced to shut production facilities in the US, UK, Brazil, India, and Russia to isolate the data servers and address the cyberattack.
- 2020—EMA COVID-19 cyberattack: Pfizer, BioNTech, and AstraZeneca had vaccine-related information hacked when an EMA server was hit by a cyberattack.
- 2020–2021—North Korean cyberattack attempts: According to *The Wall Street Journal,* North Korean actors tried to steal vaccine information from Johnson & Johnson and Novovax, as well as three South Korean drugmakers.

Establishing a cybersecurity strategy can follow a maturity model with 129 questions (available atwww.servitecno.it) as presented. Subsequently he showed the Supervisory Control and Data Acquisition (SCADA) Security Maturity Model: Phase 1: Conduct assessments and define standards; Phase 2: Conduct training and raise awareness/funding; Phase 3: Deploy cybersecurity solutions to mitigate risks; and Phase 4: Operate and maintain. The proposed standards to be used are ISO 27001, ISO 27002, ISA 99, and IEC62443. Other success factors for implementation include budget owners, management, and leaders having a mechanistic understanding and the inclusion of industrial control systems (ICS) experts whose expertise can bridge the gap between ICS and IT security.

CELL AND GENE THERAPY

Wolfram Carius, Executive Vice President, Pharmaceuticals, Bayer AG, Germany, presented "How to Make the Biorevolution a Reality?" and discussed building Bayer's cell and gene therapy (C&GT) platform. What makes C&GT so attractive is the new disease intervention mechanism, which is distinct from pharmacotherapy, he said.

In the classical molecule world, intervention is at subcellular and cellular level by interaction with a molecular target, such as a receptor or enzyme. This treatment often leads to only symptomatic and needed permanent treatment. In the C&GT world, there is a direct interaction at the genetic level, with the opportunity to cure a genetic defect. Furthermore, modified cells are employed as curative agents (such as cytotoxic T-lymphocytes to kill cancer cells) or immunomodulatory cells to treat severe diseases (such as mesenchymal stromal cells against graft-versus-host disease). Degenerative diseases can be treated with engineered stem cells with specific features (such as secretion of cytokines to restitute or regenerate original function). The success is more often curative or regenerative rather than symptomatic or merely stopping disease progression.

In summary, C&GT is a multiproduct platform that allows for the restoration of biological functionality and can treat intractable diseases. It's a multiproduct platform that allows for several "shots on goal." It offers restoration of tissue functionality in comparison to delay of disease progression (small molecules [SMOLs], big molecules [BMOLs]) and enables treatment of previously intractable diseases. It's a precision medicine with long-lasting effect (usually only one treatment is required) that allows high customization. It enables new curative potential by further enabling other processes; for example, through local payload (cytokines) delivery.

Such new products may need new concepts in quality assurance in logistics and in business models for payment, such as in

the case of personalized medicines with short shelf lives, very high development cost, and batch sizes of only one unit.

Three organizational models for a C&GT unit were considered, from full integration in existing organization including all services and support to a complete standalone unit. At the end, a mixture of both was considered best to combine the advantages and minimize the downsides of the other "puristic" models.

QUANTUM COMPUTING

Clemens Utschig-Utschig, CTO and Head of IT Technology Strategy, Boehringer Ingelheim, Austria, highlighted quantum computing and pharma. Quantum computing is a type of computation that harnesses the collective properties of quantum states such as superposition, interference, and entanglement to perform calculations. Utschig-Utschig named some use cases across the research and development value chain for quantum computing such as imaging of tissues, molecular dynamics situation, and binding affinity prediction.

In preclinical development, quantum computing can be used for side-effect prediction. In clinical development, it can be used for prediction of pharmacokinetics. However, to have a real quantum advantage in the pharmaceutical industry, there is a need to improve existing quantum algorithms, develop new quantum algorithms for many applications, and see the predicted hardware development to become reality and test heuristics. Basic research is required, but a hype could destroy quantum computing.

GENE THERAPY

Frederic Revah, CEO, Genethon, France, focused on gene therapy. There are some main principles, such as in vivo gene therapy via direct administration, where recombinant adeno-associated virus vectors are directly injected into the target organ—for example, in the treatment of muscular dystrophies, eye disorders, liver disorders, hemophilia, or Huntington's disease. Another principle is ex vivo hematopoietic stem cell transduction, where hematopoietic cells taken from the patient are transduced with an HIV-derived lentivector and reinfused for the treatment of immune deficiencies, blood disorders, and CNS lysosomal storage disease. A third example is the cancer gene therapy based on stimulation of the immune response using chimeric antigen receptor (CAR) T-cells. CAR T-cells solve a basic problem of cancer therapy, the fight against tumors, which are invisible to the patient's immune system. Gene-modified T-cells combined with synthetic anti-gene-specific receptors attack: Step 1 is sampling of patient T-cells; step 2 is ex vivo gene transfer into T-cells, allowing specific targeting to tumor cells and amplification; and step 3 is infusion of modified T-cells.

The challenge of manufacturing was summarized as "addressing the dose issue." Revah showed the bioprocess innovation in six steps: (a) yield improvement × 100; (b) improved and novel producing cells, with super-producer cells adapted to a serum-free suspension method; (c) novel transfecting agents to improve transfection, decrease plasmid needs, and improve scalability; (d) innovative plasmids that are a major cost factor by decreasing plasmid quantities; (e) innovative production platforms, including novel cell types and cell-free systems; and (f) analytical methods to improve accuracy of analyses for product and contaminants, facilitate online analysis, and decrease quantities required for quality control.

NEW EU LEGISLATION

Nathalie Moll, Director General, European Federation of Pharmaceutical Industries Associations (EFPIA), listed the EU pharma strategy's objectives, such as unmet needs and access, competitive and innovative industry, and resilience. Unmet needs and access means prioritizing unmet medical needs/antimicrobial resistance, ensuring patients' access to medicines, and ensuring affordability of medicines for patients and health systems' financial and fiscal sustainability. Competitive and innovative industry means providing a fertile environment for Europe's industry, enabling innovation and digital transformation, and a sound and flexible regulatory system. Resilience means securing the supply of medicines across the EU and avoiding shortages; providing high-quality, safe, and environmentally sustainable medicines; and enhancing Europe's health crisis response mechanisms.

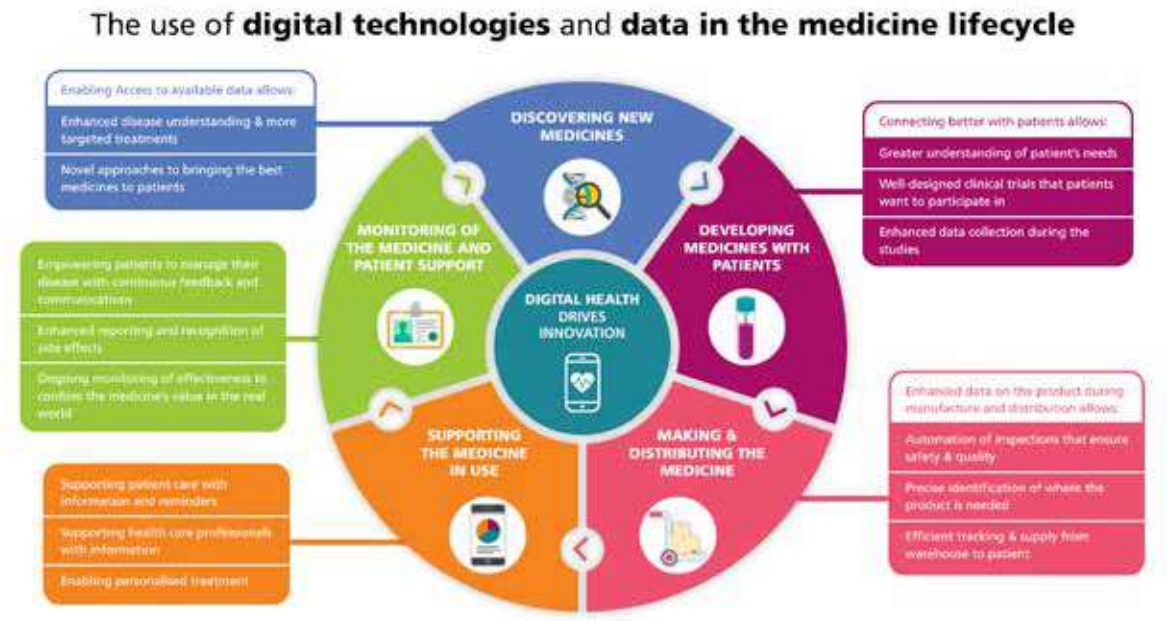
The strategy adopted in November 2020 includes as one of its pillars: enhancing resilience, diversified and secure supply chains; environmentally sustainable pharmaceuticals; and crisis preparedness and response mechanisms. Key proposals are to revise the pharmaceutical legislation to enhance the security of supply, address shortages, and report on root causes of shortages in a structured dialogue. A European Health Union package targeted for the end of 2022 will contain a regulation that extends the EMA and European Centre for Disease Prevention and Control (ECDC) mandate, regulation on serious cross-border health threats, and a new Health Emergency Preparedness and Response Authority (HERA).

The EFPIA proposals to efficiently strengthen the supply chain include a common framework, a risk-based approach, and IT and flexibility. The common framework requires a common definition of a shortages and reporting standard and a harmonized reporting system with interoperable data. A risk-based approach requires focus on the most critical products as a combination of severity for the patient, the likelihood to be in storage and the availability of alternatives; robust shortage prevention plans; and stockpiling at the EU level. IT and flexibility require electronic platform leaflets and the European Medicines Verification System for shortage prevention and monitoring. All this will be supported by digital technologies, as indicated in Figure 2.

INNOVATIVE MANUFACTURING

Evdokia Korakianiti, Head of Quality and Safety of Medicines, EMA, Netherlands, led the session "Looking into the Future: Facilitating the Use of Innovative Manufacturing Approaches from an EU Perspective." The EU vision on innovation has the following key drivers: accessibility and availability of medicines;

Figure 2: Digital technologies within the medicine life cycle (source: EFPIA, https://www.efpia.eu/about-medicines/development-of-medicines/digital-health/).



data analytics, digital tools, and digital transformation; innovation; antimicrobial resistance; supply chain challenges; and sustainability of the network and operational excellence bodies.

The defined goals and objectives for innovation are to catalyze the integration of science and technology in medicines development in three ways. First, by supporting the integration of scientific and technological progress in the development of medicines (e.g., precision medicine, biomarkers, omics, and ATMPs) and ultimately into patient treatment. Second, by implementing an EU model for efficient, timely, and coordinated horizon scanning and priority setting that fulfills the needs of regulators, health technology assessment bodies, and payers. Third, by facilitating the implementation of novel manufacturing technologies.

Korakianiti highlighted the following as innovation trends for 2025–2030: (a) gene therapy and genome editing (in vivo gene editing); (b) microbiome products; (c) digital health; (d) vaccines using novel technologies (mRNA, viral vectors, and nano-delivery systems); (e) nanomaterials for targeted and modified release formulations; (f) novel manufacturing approaches (small portable manufacturing sites); (g) decentralized manufacturing (cell processing ATMPs); (h) 3D printing; (i) end-to-end continuous manufacturing (CM); (j) automation; (k) artificial intelligence and big-data approaches (Pharma 4.0™), and (l) individualized therapies.

The defined goals for supply chain challenges are fivefold. First, enhance traceability, oversight, and security in the medicine supply chain from manufacturing to importation and final use of active pharmaceutical ingredients (APIs) and excipients. Second, enhance inspector capacity, building at EU and international level to address the problem of APIs, new technologies, and continuous manufacturing. Third, reinforce the responsibility for product quality by harmonizing and reinforcing guidance to facilitate a coherent approach to the standards by regulators and industries for medicinal products. Fourth, encourage supply chain resilience and review long-term risks resulting from dependency on limited number of manufacturers and sites to ensure continuity of supply and availability of medicinal products. Fifth, analyze the possible implications of new manufacturing technologies and adapt the regulatory framework to accommodate innovation in manufacturing and distribution of medicinal products.

Pharmaceutical legislation needs to develop as well, Korakianiti explained, stating "there are no barriers in the legislation preventing advanced manufacturing but clarifications and guidance are needed."

Korakianiti identified six main areas, with their hot topics and the regulatory environment:

1. Decentralized manufacturing: Considerations for more flexibility for manufacturing and importation authorization licenses for remote sites, better define responsibilities and duties of QP and marketing authorization holders, and supervise central and remote sites.

2. Personalized medicine: Clarify the adaptations and platform approaches permitted for such products (for example, constant

part/adapted part). Consider aspects of traceability, data privacy, pharmacovigilance, and product information. Consider manufacturing steps that may be adapted and require data requirements to justify and support proposed adaptations. Verify adaptations in GMP principles to personalized medicines. Complete batch definition and batch release.

3. Pharma 4.0™: Align expectations and definitions with other parts of the legal framework that deal with digitalization (e.g., artificial intelligence) such that it does not create a divergence. Update GMP chapters and annexes.

4. Continuous manufacturing: Currently, there are five marketing authorization applications and one variation already approved. Enable adaptations or clarifications for batch concepts. Support end-to-end CM: GMP, API, and finished product specifications. Develop control strategy digitalization and modeling.

5. General: Consider the life-cycle approach. Revisit the variation classification guideline (e.g., allow real-time changes in adaptative manufacturing processes and/or control strategies). Update assessor and inspector practices.

6. Regulatory environment: Consider multiple voices. Watch for a lack of a single engagement pathway that follows through from proof of concept at the technology level through to product development, IMP, approval, and major related life-cycle changes. Consider the overall potential of a manufacturing innovation to influence many products or if the global supply chain is not easily built into the value proposition for a single product; this includes innovative methods increasing uncertainty, risk, and cost. Regional disconnect does not facilitate global development and manufacture. Consider regulator expertise capacity and culture toward risk.

The EMA is committed to creating a regulatory environment that fosters advanced manufacturing applications. The newly founded Quality Innovation Group of EMA is a key enabler as well as the international collaboration and efforts being made within the ICH and at the International Coalition of Medicines Regulatory Authorities (ICMRA) level.

QUALITY SURVEILLANCE

Nandini Rakala, Data Scientist and Visiting Associate, Office of Quality Surveillance, Office of Pharmaceutical Quality, CDER, FDA, spoke about advancing quality surveillance. Five key areas have been highlighted: pharmaceutical quality system effectiveness, quality signal detection and topic modeling post-market quality surveillance, risk-based prioritization using machine learning, quality metrics, and quality management maturity.

Pharmaceutical Quality System Effectiveness

The strategy is to integrate advanced analytics into quality surveillance to enhance an overall proactive quality surveillance framework through the integration of predictive analytics and artificial intelligence (AI)-based machine learning (ML) techniques. Subjects will be quality metrics, quality management maturity, sites engagement program, and ongoing research exploring applications of ML to improve site selection models.

The pharmaceutical quality system (PQS) assessment framework is related to the facility (inspection and product quality defect reports) and to the historical data for performance metrics (corrective and preventive action [CAPA] effectiveness, investigation times, human error, root cause, repeat deviation, and time to initiate recall).

Assessed qualitative elements are management commitment, quality policy, quality planning, resource management, internal communication, management review, management of outsourced activities and purchased materials, process performance and product quality monitoring system, CAPA systems, change management, and continuous improvement. Modeling a pipeline for data flow and the creation of new consolidated performance metrics can lead to predictive scoring and benchmarking illustration. All data can be used!

Quality Signal Detection and Topic Modeling Postmarketing Quality Surveillance

The Office of Quality Surveillance requires a systematic and data-driven approach to identify potential quality signals in postmarket surveillance reports. The objectives are to first, identify changes in the reporting habits and product names to prioritize resources and identify potential product quality signals; and second, create a function that uses statistical process control charts to flag entities with unexpected changes in their quality defect reporting habits. In addition, there is the application of natural language processing (NLP) algorithms to discover topic clusters and commonly occurring problems across the network of regulated facilities and products.

Risk-Based Predictive Prioritization

Field alert report (FAR) prioritization is an innovative AI framework leveraging ML and NLP for risk-based prioritization of incoming initial FARs. It is applied using multidisciplinary analytics and subject matter expert collaboration by incorporating input on data cleaning, topic-keywords refinement, rare-events tagging, and risk-based target creation in a programmatic manner. There is a streamlined process of data preprocessing and developing topic model predictors, merged with other key indicator variables for predictive scoring. Insights generated by this process will be used to proactively prioritize assignments and inform key indicator variables interpreted and recommended by the data-driven machine learning hybrid model.

Quality Metrics

The quality metrics program objectives are to analyze the quality metrics data to obtain a more quantitative and objective measure

of manufacturing to ensure quality and reliability. The idea is to integrate the metrics data and resulting analysis into the FDA's comprehensive quality surveillance program. Then, apply the analysis results to assist in identifying products at risk for quality problems and to enable sustainable current good manufacturing practices (CGMP) compliance supported by continual improvement, promote an effective PQS, and mitigate drug shortages. Furthermore, the strategy is to develop compliance and inspection policies and practices to improve the agency's ability to predict future drug shortages. It is intended to be a mandatory program.

Key lessons learned from a feedback program included that cross-sectional analysis focused on comparing sites and products is not meaningful without context. It's more appropriate to evaluate site performance over time for trends, shifts, and change points. In some instances, a combination of metrics rather than a single metric was preferred to assess a particular practice area.

The FDA's analysis of the data submitted indicated the applications of statistical quality control, ML, and NLP as appropriate, and advanced analytical techniques used to assess quality metrics data submitted by industry. FDA learned that pilot firms are also deploying these techniques to monitor performance and identify signals. Certain metric calculations based on the definitions from the 2016 revised draft Quality Metrics Data guidance can result in mathematical discrepancies that are caused by inherent variabilities from real-time operations. PQS effectiveness is a critical component of a metrics program, as evidenced by numerous sites submitting data around their CAPA program, repeat deviations, and other timeliness metrics.

The proposed approach for a quality metrics reporting program includes manufacturing process performance, which includes process capability/performance indices, right-first-time rate, and lot release cycle time; PQS effectiveness, which includes CAPA effectiveness, repeat deviation rate, change control and equipment effectiveness, and unplanned maintenance; laboratory performance, which includes adherence to lead time, right-first-time rate, and calibration timeliness; and supply chain robustness, which includes on-time in-full, fill rate, days of inventory on-hand, and disposition on time.

Quality Management Maturity (QMM)

QMM is defined as a state attained by having consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement. Meeting CGMPs is the minimum standard for legally marketing drug products in the US. CGMPs assure proper design, monitoring, and controls for manufacturing processes and facilities. Fully realizing the pharmaceutical quality vision for the 21st century requires moving toward richer quality management systems.

QMM is not a discrete concept: it is a holistic concept that includes PQS effectiveness and many related aspects of business processes that enable manufacturers to proactively monitor quality-related events. Driven by management commitment, manufacturing strategies, supply chain management, quality risk management, and effective knowledge management, it results in targeted, prioritized, and risk-based mitigation plans driven by data and advanced analytics. QMM is intended to be a voluntary program aimed at recognizing and rewarding manufacturers for "mature quality systems" that achieve sustainable compliance and focus on continuous improvement, business continuity plans, and early detection of supply chain issues.

All stakeholders with oversight and controls over manufacturing take ownership for quality. Management sets the tone of commitment to quality and drives the budget, adoption, and integration of quality. Organizational objectives drive quality, thereby reducing cost of quality. Quality systems shape the manufacturing site's culture. These stakeholders should prioritize investing in people, designing an optimized patient-centric experience from the outside in, moving toward a performance-based QMM, and focusing on innovation and continual improvement, with a strong sense of change and knowledge management. They should support proactive risk management, mitigation, planning, and forecasting using application of predictive analytics and state-of-the-art optimization. Further, they should ensure there is a robust metrics program in place, driven by advanced analytical methods, sophisticated statistical tools and techniques, and AI-based technologies augmented by human intelligence. ICH Q10 and cGMPs are basic requirements for a PQS. Quality metrics are a key aspect of a mature PQS, using data-driven approaches to reduce quality issues and drive continual improvement.

Building a QMM program is bolstered by the data learned from efforts to date, such as the PDA Quality Culture Initiative, ISPE Advancing Pharmaceutical Quality Program, Quality Excellence University of St.Gallen, FDA/CDRH Case for Quality Pilot Program, Dun & Bradstreet Quality Benchmarking Study and others. The FDA initiated a QMM pilot assessment framework with six program areas: leadership and governance, operations, continual improvement, stakeholder engagement and satisfaction, knowledge management, and workforce engagement. The framework also has four pillars: sustainability, risk management, compliance, and quality culture. The outcome of these pilots have been published in an FDA white paper titled "Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals" [1].

The insights generated will be used to enhance comprehensive surveillance through proactive and risk-based data-driven decision-making. Current research indicates quality metrics as a key aspect of a mature PQS. Both strong metrics and quality culture programs are part of QMM, which assists in reducing the risk of supply chain disruptions and in fostering a culture of high quality. The FDA envisions that a QMM rating system will provide a more robust drug supply chain and greater commitment to quality in the pharmaceutical manufacturing industry, thereby leading to reduced potential for drug shortages.

CONCLUSION

The keynotes and sessions provided a wealth of information to attendees. Over 90% of the feedback collected after the conference rated the event as very good or excellent. This was primarily related to the quality of presentations, speeches, and panel discussions. The first in-person conference in years brought members and speakers together for an impactful event.

Reference

1. US Food and Drug Administration. "Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals." Center for Drug Evaluation and Research. Published 7 April 2022. https://www.fda.gov/media/157432/download

About the author

Thomas Zimmer, PhD, is ISPE Vice President, European Operations. He previously was Senior Vice President of the Corporate Division, Safety, Quality & Environmental Protection, at Boehringer Ingelheim, where he worked from 1981 to 2000 and held several positions in pharmaceutical development, pharmaceutical manufacturing, and management operations for the Americas and Europe. He was also Head of the Project Production Alliance Europe and later Head of Pharma Operations at Boehringer Ingelheim France. Thomas is Chair of the Anti-Counterfeiting Ad Hoc Group and a member of the Scientific, Technical, and Regulatory Policy Committee at the European Federation of Pharmaceutical Industries and Associations. He is Chair of the Industry Advisory Board for the Institute for Packaging of the University of Applied Sciences in Berlin, a member of ISPE's International Leadership Forum, and a board member of the Pharmaceutical Security Institute. He studied pharmacy at the Johann Wolfgang Goethe University in Frankfurt/Main, where he wrote his doctoral thesis on pharmaceutical technology.

ISPE Celebrates the 2022–2023 Board, Honor Award Winners, at Annual Meeting

By Susan Sandler

The 2022–2023 ISPE International Board took their places and the gavel passed to a new Chair during the 2022 ISPE Membership Meeting and Awards Lunch on 1 November during the 2022 ISPE Annual Meeting & Expo in Orlando, Florida.

Incoming Chair Michael L. Rutherford, Executive Director, Computer Systems Quality & Data Integrity at Syneos Health, began his year as Chair. Outgoing Chair Jörg Zimmermann, Vice President, Vetter Development Service, External Affairs, Vetter Pharma-Fertigung GmbH & Co., moves into the Past Chair position of the International Board's Officers.

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

LOOKING BACK, LOOKING AHEAD

Zimmermann opened the Membership Meeting with a look back at the year, outlining the two main projects of the Board during 2022:

- One ISPE initiative provides growth incentives for Chapters and Affiliates and benefits the Society overall. Comments on the charter have been implemented into the 2023 version.
- Strategic plan refresh for 2023–2025 adapted the existing strategic plan to encompass the Society's "very confident position: Shaping the Future of Pharma and bringing quality medicines to patients worldwide." A video was screened about strategic objectives and desired outcomes for the strategic plan, including:
  - Strategic objectives: Expand thought leadership; regular refresh of content priorities; a balanced portfolio of programs and services; diversity, inclusion, and social responsibility; foster partnerships and collaborations; strengthen member value through content and communications; attract and retain members and focus on regional needs; and digital transformation to improve industry leadership and member engagement.
  - Desired outcomes: Support of relevant therapeutic modalities in content; ISPE to remain a thought leader; evolve virtual and hybrid platforms to have global reach; grow and scale professional development programs; expand social responsibility impact; increase the ISPE Foundation donor base in programs; build partnerships that drive member value; foster regulatory interactions; grow membership to 25,000 by 2025; continue volunteer appreciation programs and elevate the value of volunteers to attract more volunteers; develop digital solutions and improve the digital experience; and increase agility to respond to current industry needs.

Zimmermann acknowledged outgoing Board members for their contributions: Joanne Barrick, Senior Director, TS/MS Validation, Eli Lilly and Company; Heather Bennett-Kelley, Project Manager/Engineer, ACCO Systems; Chris Chen, CEO, WuXi Biologics Co.

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The 2022–2023 ISPE International Board of Directors

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Timothy J. N. Watson, PhD
Executive Director & Team Leader, CMC Advisory Office
Pfizer Inc.

EX OFFICIO

Emerging Leaders Representative (non-voting)

Zen-Zen Yen
Head of Engineering
Bayer AG

2022 International Honor Awards

The 2022 ISPE Honor Awards were distributed to the recipients by Hartman, Rutherford, and Zimmermann.

2022 PROFESSIONAL POSTER DISPLAY AWARD

Andrea Sardella, PhD
Pharma Inspection Product Development
Stevanato Group S.P.A.

2022 INTERNATIONAL EMERGING LEADER HACKATHON WINNING TEAM

Clair Delmas, Anne Lynch, Emanual Montanez, Shakti Nagpal, Silas Tamufor, and Team Coach Brandi Stockton

2021 ISPE PE ROGER F. SHERWOOD ARTICLE OF THE YEAR AWARD

(awarded for *Pharmaceutical Engineering®* content published during 2021)

"Medical Device UDI Components Management in the European Union" (July-August 2021) by Laurence Azoulay, Marie Coulon, Christophe Devins, Bernard Durand, Etienne Granier, Amel Guerrida-Marchand, Ye-Lynne Lee, Valérie Marchand, Patrick Mazaud, Brigitte Naftalin, Michel Raschas, and Nadim Wardé

2022 ISPE AFFILIATE AND CHAPTER EXCELLENCE AWARD

ISPE Japan Affiliate

ISPE South Central Chapter
(Texas, Louisiana, and Oklahoma)

2022 ISPE COMMITTEE OF THE YEAR

GAMP® Global Steering Committee

2022 ISPE MAX SEALES YONKER MEMBER OF THE YEAR AWARD

Martin J. Lipa, PhD
Executive Director, Knowledge Management
Merck & Co., Inc.

2022 ISPE RICHARD B. PURDY DISTINGUISHED ACHIEVEMENT AWARD

Anthony J. Margetts, Ph.D.
Principal Consultant
Factorytalk Co., Ltd.

2022 ISPE JOSEPH X. PHILLIPS PROFESSIONAL ACHIEVEMENT AWARD

Susan W. Neadle, FAAO, FBCLA
President
Combination Products Consulting Services LLC

2022 ISPE FOYA OVERALL WINNER AWARD

Takeda Pharmaceuticals International AG TaSiVa [Pharma 4.0™ category]

Continued from page 48

Ltd.; David Doleski, Head of Global Quality Audit and External Engagement, Sanofi; and Lou Kennedy, CEO and Owner, Nephron Pharmaceuticals.

Zimmermann passed the Chair's gavel to Rutherford, ISPE International Board Chair for 2022–2023. Rutherford spoke about the year ahead, recalling his first participation with ISPE 20 years ago when he was involved in a major FDA inspection by Robert Tollefsen and Thomas Arista that significantly changed computer system validation in the industry.

"As a result, I was asked to present learning points and outcomes of that inspection at a GAMP Forum in San Francisco in January 2003. I would have never imagined that presentation, and becoming an active member in GAMP and ISPE, would have such an impact on my career and would result in me standing here as your new ISPE Board Chair. But that is what ISPE can do for its members: provide technical development and knowledge, provide the opportunity to build strong industry networks, provide a chance to give back to our industry and the patients we serve, and open up career opportunities beyond what you think are possible," Rutherford said.

In the year ahead, Rutherford pointed to the importance of supporting the One ISPE program, reconfirming the International Board's commitment to all Chapters and Affiliates including through the Board liaison program, which assigns individual Board members to each Chapter and Affiliate, and participation in local and regional events when possible. "Supporting each other and growing ISPE is the common goal for all of us."

Initiatives such as partnerships and Technology Without Borders, and leveraging established brands including Emerging Leaders, Women in Pharma™, GAMP, and Pharma 4.0™ will continue to expand the Society's global engagement, he said. New CoPs are being established, including compounding and quality. Enhanced digital solutions are coming including the web site, social media platforms, knowledge products, conferences, and professional development programs.

About the author

Susan Sandler is ISPE Senior Director, Editorial.

CoP Focuses on the Future of C&Q

By Marcy Sanford

The Commissioning and Qualification (C&Q) CoP was one of the first CoPs to be established at ISPE. One of its founding members, Steve Wisniewski, Principal Consultant, CAI, said the CoP was formed in 2004 to identify and promote more efficient approaches that resulted in pharmaceutical facilities being fit for their intended purpose.

For 2023, the C&Q CoP Steering Committee is focusing on paperless validation and Pharma 4.0™ as areas of interest. They also have plans to distribute a benchmarking survey early this year. "The goal of the survey is to establish an industry data source for current adoption rates for quality risk management (QRM) and integrated C&Q," said C&Q CoP Chair Nathan Temple, CQV Business Area Leader, CAI. "The data set will include the cost of C&Q as a percentage of total installed cost (TIC) and other metrics and KPIs. Our goal is to provide industry with the baseline data and thus the rationale to support increased adoption rates for the advanced and efficient C&Q practices contained within the ISPE *Baseline Guide Vol. 5: Commissioning & Qualification, 2nd Edition* and the *ISPE Good Practice Guide: Good Engineering Practice, 2nd Edition*."

"Regulatory compliant and efficient commercial pharmaceutical manufacturing operations are optimally achieved with the application of the body of knowledge available from the C&Q CoP," said Temple. "Beginning with the original 2001 ISPE *Baseline Guide: Volume 5–Commissioning and Qualification* V-Model approach to the 2007 ASTM E2500 QRM-based C&Q life-cycle approach and supporting ICH Q8, Q9, and Q10 Guidance, and Regulatory guidance, the C&Q CoP has traditionally taken the lead in the transformation of qualification of facilities, systems, and

About ISPE's Communities of Practice

ISPE's Communities of Practice are just one of the benefits available to ISPE members. "Communities of Practice (CoPs) are composed of ISPE members who share ideas, best practices, and their experience across a range of topics in the pharmaceutical industry," Tim Postlethwaite, Director of Technical Communities, ISPE, explained. "Often, ISPE CoPs and their steering committees spearhead the generation of our gold standard content such as Good Practice Guides, *Pharmaceutical Engineering* articles, conference presentations, and training programs." The continuing series of profiles of CoPs being published in *Pharmaceutical Engineering* recognizes the importance and contributions of CoPs to ISPE and the industry.

equipment in support of process qualification/process validation away from retrospective execution of installation qualification and operational qualification protocols to concurrent project life-cycle execution activities."

INFORMATION SHARING FORUM

Traditionally, the C&Q CoP has provided a forum where regulators, industry leaders, and stakeholders can express ideas and share best practices in support of C&Q associated with the commissioning, qualification, and validation holistic process. The CoP takes a proactive approach to knowledge development and sharing in its areas of focus through the following activities:

- Participation, as C&Q subject matter experts (SMEs), in related ISPE Baseline Guides and Good Practice Guides
- Webinars of defined areas of focus
- *Pharmaceutical Engineering*® articles
- Presentations at ISPE conferences and Affiliate and Chapter events
- Establishment of task teams with identified scopes of focus such as key deliverables associated with the quality risk management (QRM) C&Q process and paperless validation.
- Technical input and review in support on the ISPE T40, QRM C&Q training course

As new challenges occur in the pharmaceutical industry, steering committee members will look for ways to continue to discuss and develop best practices to meet industry needs. As the pharmaceutical industry begins to embrace the opportunities presented by the concepts of digital transformation, the C&Q CoP is looking to provide guidance and best practices on digitization efforts in their areas. "We anticipate additional content from the paperless validation team to include best practice blog posts, initiation of a good practice guide, and collaboration with the Pharma 4.0™ CoP on a case study," said Temple.

BENEFITS OF PARTICIPATION

Temple encourages ISPE members to get involved with the CoP by participating in the C&Q CoP Discussion Forum on ISPE Engage or joining a subcommittee or task team established by the steering committee. "I joined the steering committee in 2018 right as the team was finishing the revision to the ISPE *Baseline Guide Vol. 5: Commissioning and Qualification, 2nd Edition*. It was an exciting time and I wanted to help roll out the vision that others had so masterfully captured in this major update. We had a large group covering multiple technologies and practices; however, everyone focused on optimizing C&Q to meet the goal of equipment fit for purpose using a QRM approach. To me, there has been great value working with the CoP. It is professionally satisfying to work with such a diverse group of professionals."

C&Q Steering Committee Member Jörg Block, GMP Compliance Engineer, Bayer, joined the CoP at the ISPE Annual Meeting in 2006. "At that time, developing a balanced C&Q process providing evidence that our facilities, installations, and equipment were fit for purpose was a big effort. Besides the EU GMP Guide Annex 15, the ISPE *Baseline Guide 5* was one of the key drivers and the ICH Q9 gave the basis for the development of ASTM E2500. The draft version of ASTME 2500 was heavily discussed at the C&Q Steering Committee meeting and the annual meeting in November 2006. It has been a great value for me to be part of these discussions, to contribute but also to listen and learn from all the other perspectives that were shared. I very much appreciate the opportunities provided working with the C&Q CoP. The exchange of experiences, ideas, and results, coming to a common understanding on how to proceed and present the topics to the C&Q community, and to receive feedback provides a continuous improvement process. Through my involvement with the CoP, I've had other opportunities with ISPE to the work on guidance documents, present at conferences, and work on articles and webinars. Every experience gives me additional insight and is ultimately a benefit for my company."

For Wisniewski, the CoP is a part of the value of ISPE membership. "I attended ISPE's first Annual Meeting and have been a member since then," he said. "I joined because I supported ISPE's stated goal of supporting networking and communication between industry leaders, regulators, and those working in the pharmaceutical industry in support of the efficient manufacture of quality products. As an engineer by training, I always had a focus on manufacturing operations and the associated facilities, systems, and equipment. I realized early on that active participation in ISPE would be a benefit to me professionally and also provide an opportunity to provide a benefit to the pharmaceutical industry. Being a member of a Community of Practice is just one of the ways ISPE members can meet each other."

About the author

Marcy Sanford is ISPE Publications Coordinator.

ISPE BRIEFS



New Guide Helps Maintain and Establish PPPQMS

ISPE's new *Advancing Pharmaceutical Quality (APQ) Guide: Process Performance and Product Quality Monitoring System (PPPQMS)* focuses on the key aspects of maintaining and establishing an effective PPPQMS. An effective PPPQMS is crucial to establishing and maintaining a state of control. It enables continual improvement and is key to proactively identifying the need for product quality and process improvements.

"The PPPQMS is an element of the pharmaceutical quality system and is required for monitoring, analyzing, controlling, and improving the process performance and product quality. But what defines that system and what tools are available to support it are not always fully understood," said Guide Co-Lead Line Lundsberg, PhD, Lundsberg Consulting Ltd. "If you are on a digitization journey, this guide is essential, as it will help you by explaining the different PPPQMS elements, offers tools to assess your current maturity level, and defines the aspirational goals for an optimized system that is needed for digital and automated monitoring and control systems."

"If pharmaceutical companies do not have a system in place for monitoring process performance and product quality according to ICH Q10, they are not in regulatory compliance," said Christian Wölbeling, Executive Industry Advisor, Körber Pharma Software. "The guide describes Level 3 'Managed' in the APQ 5-Level Maturity Model as meeting the expectations of ICH Q10. This level is recommended as a prerequisite for starting the digitalization journey. Digitalization is the key to advancing the maturity of the Quality Management System from 'Managed' to the 'Improved' Level 4 and finally to the 'Optimized' Level 5."

The guide provides a quality management framework for assessing and advancing an organization's PPPQMS maturity level by evaluating the following aspects:

- Establishing a control strategy
- Determining tools for measurement and analysis of parameters and attributes
- Analyzing parameters and attributes
- Identifying sources of variation
- Including feedback on product quality from internal and external sources
- Providing knowledge to enhance process understanding

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

—Marcy Sanford, ISPE Publications Coordinator

Meet the ISPE STAFF



Jonathan Kolade

In each issue of *Pharmaceutical Engineering®*, we introduce a member of the ISPE staff who provides ISPE members with key information and services. Meet Jonathan Kolade, IT Operations Manager/IT Department.

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

The main objective of my role is to keep the ISPE IT infrastructure and services running. This includes implementing and maintaining the security, connectivity, uptime, and functionality of the technology programs, software, and hardware that we use.

What do you love about your job?

Any day of the week can introduce a diverse situation, which usually turns into an opportunity to collaborate with my team members and other colleagues in different departments. There is always an opportunity to develop personally and gain new experiences in the information technology field.

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

Working out, reading, often volunteering in my local community, teaching my kids how to play tennis, and learning to play golf. I also enjoy watching movies with the family.

RAPID FILTER OR RESIN CHANGE STRATEGIES for Biomanufacturing

By Amy Rhee, Tabetha M. Bonacci, PhD, Bradford Stanley, Greg Evangelist, John Fisher, John Armando, MSc, RAC, Yuh-Fun Maa, PhD, Asif Ladiwala, PhD, Christopher J. Dowd, PhD, Rob Deitcher, Brian Kelley, Nina S. Cauchon, PhD, William Garden, Jessica Molek, Melissa Holstein, PhD, James Angelo, Chris Gallo, Daniel LaCasse, and Glen Bolton

Pandemic-related supply chain shortages have placed constraints on the supply of essential filters and chromatography resins. An agile regulatory pathway to implement alternative filters and resins into manufacturing is necessary to ensure the continued supply of approved biologics. To allow this in the US and potentially globally, the regulatory strategy proposed in this article is to provide an appropriate characterization package to demonstrate that the alternative filter or resin has a low risk to impact product quality in a prior approval supplement (PAS), and later provide at-scale data as part of an annual report or submission at the time of distribution.

Both the development of COVID-19 vaccines and monoclonal antibody therapies and supply chain shortages related to the pandemic have affected supply of the essential filters and chromatography resins used in the manufacture of biological products. Section 101 of the Defense Production Act of 1950 was extended by Executive Order 13911 in 2020 to Respond to the Spread of COVID-19. This has allowed for regulation of the allocation of necessary supplies to the production of COVID-related therapies through rated orders [1]. The unpredictable timing of rated orders has placed constraints on filter vendors because they are unable to confirm delivery of orders needed to support manufacture of clinical and commercial biologic therapies not targeting COVID-19 [2, 3].

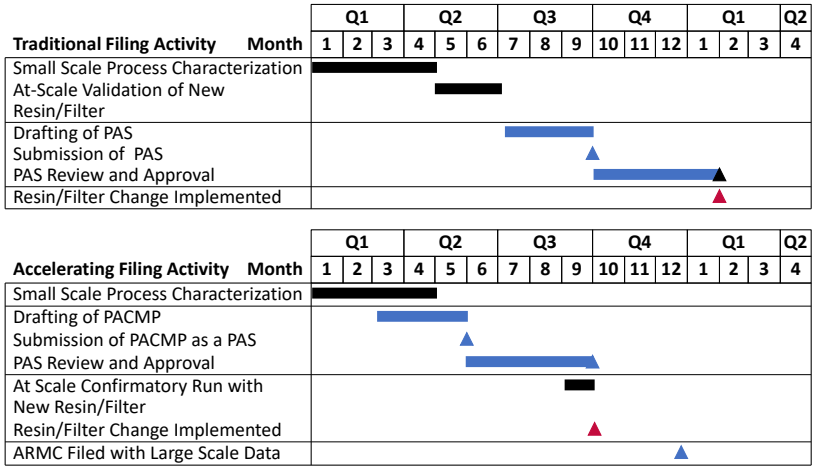
Since the start of the pandemic, companies have employed multiple risk mitigation measures to conserve supply of filters and chromatography resins. However, given the continued uncertainty in supply, use of alternative filters or resins may be necessary to ensure continued patient supply of approved biologics. For critical filters and resins in manufacturing of biological therapeutics, each health authority typically requires approval before final product distribution using alternatives.

This article presents a proposed regulatory strategy to help alleviate supply risks for approved therapeutics. The strategy is to provide an appropriate characterization package that demonstrates the alternative filter or resin will not impact product quality, submit it in a PAS, and, if needed, submit a request for an expedited review. The initial PAS would also include a commitment to provide any at-scale product quality and/or validation data in the US Annual Report of Minor Changes (ARMC) or potentially a submission at the time of distribution (changes being effected [CBE-0]). Acceptance criteria for confirmatory at-scale data would be proposed in the PAS as part of the postapproval change management protocol (PACMP). This strategy saves approximately 4 to 6 months (depending on the time required for PAS approval) before initiation of the resin and filter change, as shown in Figure 1. With the endorsement of International Council for Harmonisation (ICH) Q12 in November 2019 [4], and its ongoing implementation in ICH member countries, applying this approach has the potential for use as a global regulatory strategy.

The proposed characterization and validation plan is adequate to support approval of an alternate:

- Sterilizing-grade filter option for aseptic drug product manufacturing
- Viral filter (and potentially viral pre-filter) for drug substance manufacturing
- Ultrafiltration and diafiltration (UF/DF) membrane for drug substance manufacturing
- Protein A affinity chromatography resin for drug substance manufacturing

Figure 1: Traditional vs. accelerated filing timeline for a resin or filter change.



The proposed submission category of annual reportable for the protein A chromatography resins, filters, and other single-use raw materials is presented next. In all cases, these changes are enabled by strong product and process knowledge and mature quality systems [3, 5].

Though not the focus here, when scientifically justified, the characterization package for a given resin or filter may be used to support more than one product [3, 5]. Similarly, prior knowledge from large- or small-scale characterization or validation studies with multiple earlier products for a particular resin or filter could be used to support a current product. Details on the proposed characterization and at-scale studies to support alternative filters and resins are provided later in this article.

BACKGROUND

Companies have experienced significant procurement delays for filters and resins because of the COVID-19 pandemic. Because of rated orders and resulting prioritization, some vendors have stopped or delayed confirmation of orders, delayed previously confirmed orders, and significantly delayed deliveries. Purchase orders that were placed up to a year prior, including previously confirmed orders, are not being delivered with little to no advance notice.

Companies have proactively managed these risks to avoid drug shortages. In late 2020, many companies evaluated mitigation options across commercial and clinical portfolios to slow consumption of critical at-risk raw materials in response to early signals from suppliers on the potential impact of rated orders on their supply chains. Since the start of the pandemic, the Center for Drug Evaluation and Research (CDER) has received about 150 inquiries related to strategies for chemistry, manufacturing, and control (CMC) changes, including changes to filter suppliers, filter control strategies, and filter reuse validation [5].

The FDA has indicated it may "consider available information and approaches to mitigate the risk to product quality associated with the change to support a reporting category for certain supplements that is lower than what otherwise would be most suitable" [6]. In addition, the FDA is using multiple tools to facilitate implementation of manufacturing changes, such as risk-based reduction in supplement reporting categories and flexible assessment practices [3, 6]. With these tools, the rationale, supporting information, and risk analysis should be provided.

Within the drug substance and drug product manufacturing processes, filters are used for a variety of purposes, including non-product contact (e.g., media, buffer, and air/vent filters); product contact for process and product impurity; and bioburden and particle removal. Similarly, chromatography resins play an important role as the primary means of impurity removal and potentially viral clearance within the drug substance manufacturing process.

Given the criticality of chromatography resins and some product contact filters in meeting product quality acceptance criteria and specifications, significant process characterization is performed before a product contact filter or resin is selected. Demonstration of performance is included in viral clearance and process validation, which are submitted as part of product licensure. These characterization and qualification activities can require more than 6 months to complete.

Currently, companies are employing multiple strategies to proactively mitigate against the risks presented by resin or filter supply delays or disruptions, for example:

- Communicating critical resin and filter demand requirements to suppliers
- Developing an approach to extend expiry and the number of reuses for reusable resins and filters, such as tangential flow filtration (TFF)
- Pursuing alternate sourcing and substituting at-risk filters/resins with alternates

- Adjusting manufacturing schedules to accommodate late deliveries of resins and/or product contact filters

Given the uncertainty of how long and to what extent resin and product contact filter supply delays may continue, companies intend to implement alternative resins and filters to mitigate risk to product supply and ensure continued supply to patients in need.

DISCUSSION

Several different protein A affinity resins are commercially available that leverage the highly selective binding of immobilized protein A ligands to the Fc region of monoclonal antibodies and other Fc-containing molecules (e.g., fusion proteins). The majority of the studies performed to qualify an alternate protein A resin can be completed using a suitable scale-down model before introducing it into full-scale production (e.g., process characterization; process linkage, cleaning, and reuse). Essential performance characteristics can also be evaluated by those with prior knowledge (including platform knowledge) using additional small-scale studies before full-scale production.

Filters and other single-use components are essential to production of biological therapeutics. Although their importance is paramount to ensuring supply of quality product, their function and critical requirements are relatively well-understood. Alternate suppliers of equivalent filters/components with comparable critical material attributes (e.g., membrane material, pore size) are also well-known. Most studies performed to qualify an alternate filter or component can be completed before the alternate component is introduced into full-scale production (such as microbial ingress, extractables/leachables, compatibility, adsorption studies, and virus clearance studies, if applicable). Vendor studies supplemented by additional small-scale studies performed by companies enable the evaluation of essential performance characteristics before full-scale production. Changes that typically require health authority approval before use include changes to filters (final drug product or drug substance filtration, viral filtration, UF/DF) and to protein A affinity resin.

The intended qualification approach begins with a brief outline of the purpose of the step and change proposed. Next, a description of the characterization studies and supporting small-scale studies would be provided in a PACMP, which would be filed as a PAS [5]. The PACMP would outline plans for confirmatory at-scale production runs and predefined acceptance criteria, which is aligned with the ICH Q12 guidance and recent FDA presentations [3, 5, 6]. Third, confirmatory at-scale data would be submitted via the US ARMC. For older processes, process characterization and any impacts on product quality may be assessed using updated analytical methods, if applicable. Finally, a commitment may be provided to put the first post-change drug product lot (and drug substance lot, if the drug substance is liquid) on stability as an ad hoc lot, in addition to the typical annual stability measurements, based on the potential of the change to impact attributes that may be impacted by stability testing.

Table 1: Comparison of proposed filter alternatives for sterile filtration steps in the drug product manufacturing process.

Details	Approved Filter	Proposed Filter Option 1	Proposed Filter Option 2
Supplier	1	2	3
Membrane material	Single- or dual-layer hydrophilized PVDF (or PES)	Single- or dual-layer hydrophilized PVDF	Single- or dual-layer hydrophilized PES
Nominal pore size	0.22 or 0.2 µm	0.22 or 0.2 µm	0.22 or 0.2 µm
Sterilization method	Autoclavable	Autoclavable or Gamma-irradiated	Autoclavable or Gamma- irradiated
Filtration time	≤ 72 hours	≤ 72 hours	≤ 72 hours
Filtration temperature	2°C to 30°C	2°C to 30°C	2°C to 30°C
Maximum filtration pressure	15 psig	15 psig	15 psig

PVDF = polyvinylidene fluoride, PES = polyether sulfone

In addition to these changes (which are typically completed prior to approval), alternate sources for other product contact filters and single-use components may be reported via the ARMC or a CBE-0 before implementation, provided they have minimal or no impact to typical details provided in Module 3 of a Biologics License Application (BLA), based on risk assessments.

The accelerated filing proposal provided in this article could speed up the time to implementation of an alternate filter or resin by 4 to 6 months compared to a traditional filing, as shown in Figure 1. However, 12 months are typically required before implementation, even when using the accelerated filing. It is possible that in some cases where resin and filter supply risks pose an imminent threat to drug supply, more rapid use of alternative filters and resins will be required. In these cases, companies can consider filing small- and/or pilot-scale characterization data, risks assessments, prior knowledge, and vendor data as a CBE-30 before implementation at scale. Large-scale implementation would be managed through the product quality system and reported via the ARMC. Consideration would have to be given to established process conditions.

This approach would allow implementing alternative resins and filters within 6 months and would provide a rapid method of alleviating supply constraints; therefore, it would merit prior discussion between agencies and manufacturers. Four proposed data packages and submission strategies follow.

Alternative Bioburden and Sterile Filtration Filters

The filtration step is critical for aseptic manufacturing of parenteral drug products. Filter performance (i.e., microbiological control, no product impact) is determined by membrane material,

Table 2: Proposed process characterization studies to support alternative bioburden and sterile filter options.

Characterization Study	Proposed Filter Alternates	Study Description
Filterability	1, 2, 3 (Scale-down filter)	Scale-down study using alternative filters would be used to confirm no practical change in filterability of the product and confirm the appropriate filter size needed for currently validated batch sizes.
Product quality impact from filtration	1, 2, 3 (Scaledown filter)	Scale-down study would demonstrate no product quality impact due to filtration and contacting alternative filters for the maximum validated filtration time.
Initial surfactant/protein binding to filter	1, 2, 3 (Scale-down filter)	Surfactant and protein adsorption on alternative filters are expected to be similar to the approved filter due to the use of the same filter membrane material. Adsorption data would still be evaluated in separate, filter-specific studies using scale-down filters. Data would be used to assess any changes in the strategy for ensuring acceptable product quality at the start of filtration (e.g., discarding or refiltering the initial filtrate).

Table 3: Proposed filter validation studies to support alternative sterile filter options.

Study	Proposed Filter Alternates	Study Description
Microbial retention	1, 2, 3 (Scale-down PVDF filter)	This scale-down study would mimic the worst-case processing condition for alternative filter options. Alternatively, because of the potential long lead time of this study, a risk assessment can be leveraged based on vendor information and prior knowledge regarding microbial retention to justify the manufacturing use of the alternative filter at target conditions. This study can be performed in parallel with data submitted later to justify filtration process parameter acceptable ranges.
Filter leachables/ extractables	1, 2, 3	This study would be performed for alternative filter options using the sterile filtration method used during commercial manufacturing.

pore size, and effective filtration area. The qualification and validation of alternate filters for bioburden reduction filtration and sterile processing steps may be necessary for aseptic processing of commercial antibodies.

The alternative filters could be sourced from the same or a different vendor, but otherwise would generally have similar pore sizes, a similar effective filtration area, and similar acceptable ranges of relevant filtration process parameters. A technical and risk assessment of the physical characteristics, material of contact, and performance and filterability data would be performed to demonstrate that the replacement filters meet all acceptance criteria of approved filters used for drug product manufacturing when operated within the acceptable range of process parameters. A comparison of the proposed filter options is shown in Table 1.

Proposed characterization

Tables 2 and 3 summarize the proposed process characterization and filter validation studies needed to support the use of alternative filters for bioburden reduction and sterile filtration steps.

The maximum filtration time that is established based on the media fill validation and the filter validation package would be applied to the new alternative filters. Additionally, companies would perform at least one at-scale process confirmation run per product incorporating the new alternative filter or filters to confirm no impact to the drug product manufacturing process and product quality attributes (e.g., via lot release or homogeneity of critical product quality attributes throughout the batch).

Compared to inline sterile filtration, bioburden reduction filtration is further away from the final product and, therefore, is less critical to product quality. If different filters for bioburden reduction filtration and sterile filtration are used during drug product manufacturing, the acceptability of the alternative filter options for bioburden reduction filtration can be assessed based on prior knowledge with limited product-specific characterization data. The alternative filters for sterile filtration are more critical (immediately before the filling operation) and require a more rigorous data package.

The microbial (bacterial) retention ability of a sterile filter is critical to ensure product sterility. Microbial retention validation, typically performed in a scale-down study with a long lead time (6 to 12 months), can be a major bottleneck to the submission of the data package. In this case, it is proposed that a manufacturing-scale study be performed at target conditions for initial submission with the microbial retention validation data package to be submitted later to justify process parameter acceptable ranges.

Proposed submission strategy

A PACMP as a PAS would be submitted. It would contain the description of the assessment for confirmatory testing at scale and provide the following data:

- Process characterization data from scale-down studies, as described in Table 2.
- Filter validation data, as described in Table 3.

Upon completion of the confirmatory at-scale testing, where the predefined acceptance criteria in the PACMP are met, companies would provide this data in a subsequent ARMC for the corresponding product to support the pre-filter and filter changes.

In the event that filter shortages only impact the bioburden reduction filter (not the final sterile filter), internal characterization would be performed (Tables 2 and 3), and the change would be reported in the ARMC. This approach is aligned with guidance presented recently by the FDA. Making changes to a drug substance bioburden reduction filter would involve a subset of the activities required for a drug product sterilizing filter and is described as follows.

Alternative Viral Filtration Filters

Multiple commercial molecule programs may be impacted by insufficient supply of viral filters (VF). The VF step is a filtration process designed to remove potential viruses through size exclusion. The VF step may be a two-stage filtration, with a pre-filter, followed by a virus filter.

To address VF filter supply limitations across manufacturing, registration of an alternate pre-filter in addition to the approved pre-filter may be appropriate. The virus pre-filter from alternative vendors would be characterized and implemented at-scale. Comparison of currently approved and proposed VF pre-filters (Table 4) and filters (Table 5) are shown here.

Proposed submission strategy

A PACMP as a PAS would be submitted. It would contain the description of the assessment for confirmatory testing at scale and provide the following data:

- Lab-scale characterization data supporting the acceptance criteria for performance indicators and process parameters of the alternate pre-filter and filter. Characterization studies would include a demonstration of suitability via acceptable performance indicators. Qualification of a scale-down model may not be necessary or may be performed later using large-scale data for comparison. In addition, the studies would confirm the appropriate pre-filter and viral filter area needed for the viral filtration step and confirm no impact to product quality.
- The filter leachables and extractables would be assessed leveraging vendor data. The risk assessment would also be updated, if required.
- Viral clearance study data demonstrating effective virus removal. Use of a worst-case virus (mouse minute virus [MMV]) to assess virus clearance of the VF step for each product under challenging conditions (e.g., high volumetric loading) should be submitted to ensure viral clearance meets or exceeds a robust level reduction (4 $\log_{10}$) of small, non-enveloped viruses.

Viral clearance studies would demonstrate that the primary function of viral clearance is achieved. The lab-scale studies would confirm there is no product impact with use of the proposed alternate filters.

Upon implementation of the alternative filters into full-scale manufacturing, confirmatory testing would be performed on one batch at manufacturing scale. The at-scale data supporting the VF pre-filter and filter changes would likely include volumetric flux, volumetric throughput, integrity test value, and assurance that all release specifications and process controls are met. The data would be provided in a subsequent ARMC.

Table 4: Comparison of approved and proposed VF pre-filters.

Details	Approved Pre-Filter	Proposed Pre-Filter Option 1	Proposed Pre-Filter Option 2
Supplier	1	2	3
Filter media	Cellulose, inorganic filter aid	PES	Nylon

PES = polyethersulfone

Table 5: Comparison of approved and proposed VF filters.

Details	Approved Filter	Proposed Filter Option 1	Proposed Filter Option 2
Supplier	1	2	3
Filter media	PES	PES, PVDF, or cellulose	PES, PVDF, or cellulose
Nominal pore size	≤ 20 nm	≤ 20 nm (e.g., 15 nm, 20 nm)	≤ 20 nm (e.g., 15 nm, 20 nm)

PES = polyethersulfone, PVDF = polyvinylidene fluoride

Alternative Tangential Flow Filtration (UF/DF) Membrane

Multiple product programs could be impacted by insufficient supply of the UF/DF membranes. UF/DF steps are typically designed to buffer exchange product pools and to concentrate to the drug substance target concentration. The UF/DF filter retains the product protein and allows smaller salts and liquids to pass through. To address UF/DF filter supply limitations, registration of an alternate UF/DF filter in addition to the approved filter may be appropriate to mitigate filter supply risk.

A comparison of an approved and proposed UF/DF filter is shown in Table 6. A technical and risk assessment of the physical characteristics of the alternative filters should demonstrate that they are comparable or superior to the current approved UF/DF filter. Analysis and historical knowledge can be used to assess that no impact to product quality is expected.

Proposed submission strategy

Evidence for filter suitability and no product quality impact, which would include data from the filter manufacturer and data from scaled-down development studies, would be submitted as a PAS. The following would be provided:

- Lab-scale characterization data to support the acceptance criteria for performance indicators, process parameters, cleaning, and filter reuse. Characterization studies using a scale-down model and a demonstration of comparable properties via acceptable performance indicators would be submitted. In addition, the

Table 6: Comparison of approved and proposed UF/DF filters.

Details	Approved Filter	Proposed Filter Option 1	Proposed Filter Option 2
Supplier	1	2	3
Filter media	Regenerated cellulose or PES	Regenerated cellulose	PES
Molecular weight cut-off	30 kDa	30 kDa or lower	30 kDa or lower

PES = polyethersulfone

Table 7: Comparison of approved and proposed protein A affinity resins.

Details	Approved Protein A Resin	Proposed Protein A Resin Option 1	Proposed Protein A Resin Option 2
Supplier	1	2	3
Ligand	Recombinant (wild type) or engineered protein A	Recombinant (engineered) protein A	Recombinant (engineered) protein A
Backbone	Controlled pore glass or cross-linked agarose	Cross-linked agarose	Cross-linked agarose

characterization study would confirm the appropriate filter size needed for the UF/DF step and confirm no impact to product quality.

- The filter leachables and extractables would be assessed leveraging vendor data. The risk assessment would also be updated, if required.
- Additional characterization data to support cleaning and reuse of membranes for the filter lifetime study, supported with at-scale data. It is possible that the cleaning method for the new filter will differ from the legacy cleaning. Measurements of attributes indicative of microbial control (bioburden and endotoxin) would be performed in addition to process performance indicators to confirm cleaning and use after storage.

Characterization data would ensure the UF/DF step meets the desired purpose of buffer exchange and/or concentration of the protein to prepare for drug substance formulation. The lab-scale cleaning studies would demonstrate no product impact with filter reuse.

Upon approval of the PAS, confirmatory at-scale data supporting the UF/DF filter change would be provided in a subsequent ARMC. Confirmatory at-scale filter cleaning and reuse data up to the maximum characterized number of uses would be provided as the manufacturing schedule allows through a future ARMC.

Alternate Protein A Affinity Chromatography Resin

Multiple product programs are likely to be impacted by insufficient supply of the protein A resin. To address protein A affinity resin supply limitations, registration of an alternate protein A resin in addition to the approved resin may be appropriate to mitigate supply risk.

Product-specific data and historical knowledge with other products (i.e., prior knowledge), vendor data, and risk assessments can be used to determine that no impact to product quality is expected when operated within the acceptable range of process parameters. A comparison of the proposed resin options is shown in Table 7.

Proposed submission strategy

A PACMP as a PAS would be submitted. It would contain the description of the assessment for confirmatory testing at scale and provide the following data:

- Data from characterization studies (including downstream process linkage) demonstrating comparability of product quality. This includes lab-scale characterization data to support the acceptable ranges for process parameters (including resin cleaning and reuse). Qualification of a scale-down model may not be necessary or may be performed later using large-scale data for comparison.
- The resin leachable and extractables would be assessed leveraging vendor data. The risk assessment would also be updated, if required. The leaching of protein A ligand would be measured as part of the characterization and at-scale studies using an assay appropriate for detection of the specific ligand would be performed.
- Additional characterization data to support cleaning and reuse of resin for the lifetime study, supported with at-scale data.
- Viral clearance study data demonstrating effective virus removal (if applicable).

Characterization data would ensure the protein A affinity chromatography step meets the desired purposes of the step: product capture, product concentration, and initial purification. The lab-scale cleaning and lifetime studies would demonstrate no product impact throughout the life of the resin.

Upon implementation of the alternative resin into full-scale manufacturing, confirmatory testing would be performed on one batch at manufacturing scale. The at-scale data supporting the resin change would likely include yield, purity, operating conditions, and assurance that all release specifications and process controls are met. Upon completion of the confirmatory at-scale testing where the predefined acceptance criteria in the PACMP are met, companies would provide this data in a subsequent ARMC for the corresponding product to support the resin change.

Confirmatory at-scale resin cleaning and reuse data up to the maximum characterized number of uses would be provided as the manufacturing schedule allows through a future ARMC. This approach may also be employed for other chromatography steps if the alternate resin can be implemented with minimal impact to process parameters and the downstream process [3].

Other Alternative Filters and Single-Use Components

To address potential supply constraints throughout manufacturing, an evaluation of alternatives for several product-contacting filters would also be performed. The key information and data needed to assess the suitability of these filters would be evaluated before use in production.

Example 1: Depth filters

Proposed change: An alternative depth filter for direct cell capture or post-centrifuge harvest operations would be added. All registered process parameters and performance indicators would remain within the currently approved characterized range.

Characterization studies would include a combination of existing vendor and internal lab-scale studies. To establish equivalency, an assessment would be performed against the following key parameters:

- Filter capacity
- Permeability
- Yield
- Extractables/leachables
- Impact to levels of process-related impurities

Based on the analysis and available small- and large-scale data, the alternative filter would be used interchangeably with the approved filter in depth filtration operations.

Module 3 impact: An update to the list of raw materials may be required. Conclusion: Successful completion of the technical assessment, risk assessment, and characterization studies before implementation would ensure that this change has minimal potential to impact product quality, and this change would be summarized in the ARMC.

Example 2: Product Contact Bioburden Reduction Filters

Proposed change: An alternate source for the product contact bioburden reduction filters, typically used before and after each unit operation throughout the drug substance process, would be added.

Evaluation to be completed before implementation: The performances of two 0.2-micron filters would be compared based on filter sizing studies of several in-process streams. The comparison of the two filters for in-process and drug substance final filtration would be experimentally assessed against the following key parameters: filter capacity and permeability.

Vendor data for the following attributes would be assessed and considered during a risk assessment: Retention rating; extractables/leachables; and sterilization method.

The extent of the comparison could vary depending on the perceived level of risk. Filters upstream in the process, followed by several bind-elute separation steps may present a lower risk than a filter used for a liquid drug substance. Based on the analysis and available data, the alternative filter could be used interchangeably with the approved filter in UF/DF recovery filtration and drug substance final filtration. Filter sizing would depend on the capacity as determined by the applicable small-scale model.

Module 3 impact: An update to the list of raw materials may be required. Conclusion: Successful completion of the characterization studies before implementation would ensure this change has minimal potential to impact product quality, and this change would be summarized in the ARMC.

CONCLUSION

To mitigate COVID-related or similar supply challenges, a strategy is proposed herein to generate a robust characterization package designed to demonstrate an alternative protein A affinity chromatography resin, filter, or component have low risk of product quality impact and submit this data/information as a PAS with a PACMP, and, if needed, request an expedited review. In addition to characterization data, confirmatory at-scale data would be proposed in the initial PAS and a commitment would be made to provide any at-scale product quality and/or validation data in the ARMC.

For new BLA submissions (non-COVID therapies), sponsors might consider describing one or more of the alternate filter or resin strategies as a PACMP. Lab-scale characterization data in the BLA could be sufficient to support the proposed full-scale testing plan and then reporting with the ARMC, without the need for a PAS.

Although supply chain shortages for filter components are of particular concern in the US, the pandemic has highlighted the interconnected nature of global manufacturing and supply chains in the biotechnology industry. For manufacturers that have products registered in many markets worldwide, the challenges with long and uncertain delivery times for essential components such as filters and critical raw materials are exacerbated by the complex regulatory processes already inherent in the management of postapproval CMC changes [7].

For a single change that requires prior approval, the divergent data requirements, staggered submission and bundling strategies, and spread-out approval timelines in the different markets often mean that implementation takes several years. During this time, the manufacturer would be required to manage pre- and post-change product tightly to maintain compliance, often resulting in duplication of efforts and potential stockouts in cases of shortages of critical materials. It would thus be desirable to apply the regulatory strategy approaches described in this article for the FDA to other regulatory submissions.

With the endorsement of ICH Q12 in November 2019, and its ongoing implementation in the ICH member countries, this becomes a feasible global regulatory strategy [3–5]. PACMPs are typically among the first ICH Q12 tools to be used once the individual regulatory frameworks have been adapted accordingly and are already accepted in several other countries. Thus, it should be possible to gain regulatory agreement via a PACMP (which would include laboratory-scale characterization data, risk- and

science-based justifications, and appropriate acceptance criteria) that at-scale data could subsequently be submitted using a "notification low" category as per the harmonized ICH Q12 guideline. In turn, shortening the approval timelines globally will streamline the postapproval change management processes and mitigate the risk of drug shortages.

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About the authors

Amy C. Rhee is a Senior Manager, Regulatory Affairs CMC at Amgen, Inc. She received her BA from Washington University at St. Louis and an MS in RNA molecular biology from Case Western Reserve University.

Tabetha M. Bonacci, PhD, is a Director in Regulatory Affairs-CMC at Amgen, Inc. Tabetha holds a BS in biology and chemistry from St. Norbert College and a PhD in pharmacology from the University of Rochester.

Bradford Stanley is the head of downstream process development at Biogen.

Greg Evangelist works in the downstream processing group as a Senior Engineer III, where his responsibilities are developing early- and late-stage processes for the manufacturing of mAbs, Fc fusion proteins, bi-specifics, and biosimilars.

John Fisher is a Principal Engineer in the purification development and process virology groups at Genentech, a member of the Roche Group. John obtained a BS in chemical engineering from the University of California at Berkeley.

John Armando, MSc, RAC, has a MSc in chemical and biological engineering from Tufts University and an MSc in regulatory affairs from Northeastern University. He is an Associate Regulatory Program Director in pharma technical regulatory.

Yuh-Fun Maa, PhD, is a chemical engineering PhD and a Senior Principal Engineer in pharmaceutical development at Genentech/Roche.

Asif Ladiwala, PhD, is a Senior Principal Engineer and Senior Group Leader with the purification development group at Genentech. He has a PhD in chemical engineering from Rensselaer Polytechnic Institute.

Christopher J. Dowd, PhD, has a BE in chemical engineering and molecular biology from Vanderbilt and a masters' degree and PhD in chemical engineering from MIT. He is Executive Director of Genentech's Purification Development Department.

Rob Deitcher earned his doctorate in chemical engineering from the University of Virginia. He is Director, Drug Substance Technology Transfer, at VIR Biotechnology.

Brian Kelley is the Senior Vice President of Process Development at VIR Biotechnology. He obtained his BS in chemical engineering from the University of Wisconsin–Madison, and his PhD from MIT.

Nina S. Cauchon, PhD, is a Director in Regulatory Affairs–CMC at Amgen, Inc. She holds a PhD in medicinal chemistry from Purdue University. She has been an ISPE member since 2017.

William Garden is Director of Regulatory CMC at Amgen, Inc.

Jessica Molek is Director of MSAT Specialty External Manufacturing at GSK. She received her PhD in chemical engineering from Penn State University.

Melissa Holstein, PhD, is an Associate Director in the biologics development group at Bristol Myers Squibb. She received her PhD in chemical engineering from Penn State University.

James Angelo holds a BS and PhD in chemical engineering from Rensselaer Polytechnic Institute and the University of Delaware, respectively. He works at MilliporeSigma on research and development of integrated purification process solutions in the biopharmaceutical space.

Chris Gallo received a BS in animal science and an MS in biochemistry from the University of New Hampshire and a PhD in biochemistry from the University of California at Davis. He is Senior Director within BRD, focused on drug substance regulatory strategy.

Daniel LaCasse has a BS in chemical engineering from RPI. He is Senior Principal Scientist, biotherapeutics R&D, at Pfizer.

Glen Bolton is an Executive Director at Amgen, where he leads the late-stage biologics development group. Glen earned his BS in chemical engineering at UCLA and MS and PhD in biochemical engineering at MIT.

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LIFE-CYCLE APPROACH
to Cleaning Topical Drug Products

By Dijana Hadziselimovic, Kamini Rao, PhD, LSSBB, Nicole Granda Alvarez, Paul Lopolito, and Steven Robbins

Topical drug products and cosmetics are often manufactured in the same facility under a unified quality standard that supports the topical drug products' performance and label claims. Cleaning is an important component of a manufacturing process, and the process life-cycle approach should be followed for cleaning validation [1, 2]. This article explores the life-cycle approach to cleaning topical drugs and cosmetics with attention to the cleaning design phase and leveraging this information, including lab studies and pilot runs, for qualifying and monitoring the cleaning process.

The ideal case is a site using one cleaning procedure with an acceptable set of critical cleaning parameters (CCPs) for all products. However, some of the products manufactured in a topical drug facility can be difficult to clean. For example, the equipment for blending and packaging large-volume, high-viscosity formulations is complex, and the residues can be challenging to remove. Therefore, understanding and designing an effective cleaning process through laboratory testing, field trials, equipment designed for cleanability review, and risk assessments is critical to reducing resources and costs associated with cleaning validation and monitoring activities at the facility.

The cleaning validation life-cycle approach consists of three stages: design, qualification, and continued verification [3, 4]. Stage one: design, includes cleaning agents and suppliers, critical parameters and cleaning methods, laboratory and pilot testing, utility considerations, process equipment design review, cleaning process map, analytical test method validation, residue limits, visual inspection, and operations partnership.

Often referred to as the validation stage, stage two: qualification confirms that the cleaning procedure under normal conditions meets preestablished acceptance criteria [5]. It includes cleaning validation master plan, product risk assessment, utility and equipment readiness, analytical method readiness, sampling site selection/grouping, standard operating procedures, validation protocols, execution of validation protocols, personnel training, and the validation documentation package. Stage three: continued verification includes periodic review, process control, continuous monitoring, preventive maintenance, and periodic revalidation (if applicable).

The cleaning process design involves reviewing the equipment, utilities, wastewater concerns, nature of residue, selection of cleaning agent, cleaning parameter, analytical method, and sampling method. Application of laboratory testing and field testing can be used to determine why selected conditions are used for the qualification stage but not the monitoring stage. Various CCPs may include, but are not limited to, cleaning concentration, temperature, wash time, water quality, surface material, and dirty hold time.

This article explores the life-cycle approach to cleaning topical drugs and cosmetics with attention to the cleaning design phase and leveraging this information, including lab studies and pilot runs, for qualifying and monitoring the cleaning process.

CLEANING PROCESS DESIGN

Cleaning Agents and Suppliers

Topical drugs and cosmetic products contain a wide range of components based on the desired properties of the products. These components can have poor solubility in solvents such as water and can be challenging to clean. Choosing an appropriate cleaning agent and supplier is critical to having an effective and efficient cleaning process. Like cosmetics, cleaning agents may be formulated chemistries that may contain several components to ensure broad effectiveness. They may, for example, contain components such as surfactants and chelants to help remove insoluble residues and drug actives to acceptable limits. It is also essential to understand the cleaning agent rinse profile, analytical methods for residue detection, and detergent toxicity profile. The supplier's manufacturing process should provide a consistent product, quality expectations, and technical assistance to support the cleaning agent's application within cGMP facilities.

Critical Parameters and Cleaning Methods

Laboratory testing is the first step in defining the critical parameters for removing process residues before materials are taken to the manufacturing floor. Critical parameters include time, action, concentration, and temperature (TACT), as well as water quality, surface, soil load and condition, and environmental factors [6].

Table 1: Laboratory cleaning trials.

Sample	Cleaner	Cleaning Method	Concentration	Time per Cleaning Method (min)	Visual Observations	Water-Break-Free	Temp (°C)
Mineral Sunscreen	Formulated cleaner containing potassium hydroxide and detergent additive	AI, SW, CF	3% v/v + 3% v/v	45	Visually clean	Yes	80
PGL Polymer	Formulated cleaner containing potassium hydroxide and detergent additive	AI, SW, CF	5% v/v + 5% v/v	60/30/60	Visually clean	Yes	80
Allianz OPT	Formulated cleaner containing potassium hydroxide and detergent additive	AI, SW, CF	3% v/v + 3% v/v	60/30/45	Visually clean	Yes	80
Deodorizing Body Spritzer	Formulated cleaner containing potassium hydroxide	AI, SW, CF	2% v/v	15/3/30	Visually clean	Yes	60
Perfume Compound	Formulated cleaner containing potassium hydroxide	AI, SW, CF	1% v/v	10	Visually clean	Yes	60
Waterproof Mascara	Formulated cleaner containing potassium hydroxide and detergent additive	AI, SW, CF	2% v/v + 2 % v/v	60/45/60	Visually clean	Yes	60
Foundation	Formulated cleaner containing potassium hydroxide and detergent additive	AI, SW, CF	2% v/v + 2% v/v	60/30/60	Visually clean	Yes	60
Serum	Formulated cleaner containing potassium hydroxide and detergent additive	AI, SW, CF	2% v/v + 2% v/v	15/15/15	Visually clean	Yes	60
Concealer	Formulated cleaner containing potassium hydroxide	SW (52 psi)	3% v/v	45	Visually clean	Yes	80
Lip Gloss	Formulated cleaner containing potassium hydroxide and detergent additive	SW, CF	2% v/v + 2% v/v	75/60	Visually clean	Yes	80
Deep Cream	Formulated cleaner containing potassium hydroxide	SW (52 psi)	3% v/v	15	Visually clean	Yes	80
Foundation	Formulated cleaner containing potassium hydroxide	SW (52 psi)	3% v/v	30	Visually clean	Yes	80
Gel Cleanser	Formulated cleaner containing potassium hydroxide	AI, SW, CF	1% v/v	15/15/15	Visually clean	Yes	60
Clear Proof Face Mask	Formulated cleaner containing potassium hydroxide	AI, SW, CF	5% v/v	90/30/60	Visually clean	Yes	80

AI – agitated immersion, SW – spray wash (11 psi), CF – cascading flow (0.5 gal/min)

When designing the study, it is crucial to mimic plant conditions and restrictions as accurately as possible and to consider the method of cleaning. Most cleaning under consideration is for a clean-in-place (CIP) application, which consists of a spray impingement and cascading flow in the production vessel and turbulent flow through pipes and cleaning circuits [7].

The following procedure is used throughout the studies [8]:

- Step one: Dry, clean 304 stainless steel coupons (7.5×15 cm size) with a 2B finish are weighed on an analytical balance (±0.1 mg) to obtain the pre-coating weight. This step establishes a baseline weight for the coupon, and will help determine how much residue should be coated on the coupon. In addition, the weight of the dried coupon will be used for comparison to all future weights after a simulated cleaning process.
- Step two: The coupons are coated with samples. The amount of residue per surface area is controlled and recorded.
- Step three: The conditioned coupon is weighed on an analytical balance to determine the pre-cleaning weight.
- Step four: Each coupon is cleaned with agitated immersion, spray wash, and cascading flow. Agitated immersion testing is usually the best method to determine cleaning chemistry, concentration, time, and temperature. The primary cleaning effect is caused by the chemical action of the cleaning agent. Spray wash is performed in a modified washer/disinfector or washer at 76 kPa (approximately

11 psi). Cascading flow is performed at 2 L/min (approximately 0.5 gal/min). These procedures simulate the expected cleaning process. If needed, higher pressure or flow rate is evaluated. If a spray ball apparatus is used for cleaning, spray impingement and cascading flow represent spray ball cleaning.

- Step five: Each coupon is removed at selected time points and visually observed for cleanliness.
- Step six: Each coupon side is rinsed with tap water for 10 seconds at a flow rate of 2 L/min. The temperature of the tap water is 20°C to 25°C unless specified otherwise.
- Step seven: Each side of the coupon is rinsed with deionized water and examined for a water-break-free surface. Water-break-free is a qualitative test that indicates the cleanliness of a metal surface. On a clean surface, free from organic residue, water sheets evenly—without any breaks in the water film as it runs from the surface of the metal panel.
- Step eight: Coupons are dried and then weighed on an analytical balance to determine the post-cleaning weight. The coupon is clean if it was (a) visually clean and (b) water-break-free, and (c) if its pre-coating and post-cleaning weights are equal (0.0 mg residue).

Laboratory and Pilot Testing

With multiple, complex products manufactured on the same equipment, the approach is to choose the most difficult to clean products to help narrow laboratory testing to approximately 25–30 samples. The primary benefit of lab testing is to provide a starting point for CCPs (action, temperature, time, and concentration). These data become the basis for the cleaning cycle development at the pilot scale. An additional benefit of lab testing is to enable the initial creation of a grouping strategy or product families for pilot-scale work. Because there are products with active pharmaceutical ingredients (APIs) in the families (FDA-regulated topical drug products), the grouping strategy helps in the later stages of this work's validation phase.

A 125 L pilot unit of the Symex system is used for development work to enable scaleup to the production systems. Given the short development window of six months, a parent-child model is used for our product portfolio of more than 300 products. The 300 products have been narrowed down to about 60 selected products during the developmental phase and grouped into families. The goal in the design phase is to create a program that would allow for a seamless transition to validation and monitoring.

Utility Considerations

The system's key utilities are city water (hot and ambient), purified water (ambient), steam (heating the system), chilled water (cooling the system), and compressed air (controlling valves). The cleaning cycle uses city water (process water) for the initial rinse, wash, and sanitization cycles. The post-sanitization cycle uses purified water to heat the system for the final vacuum drying step.

The system is piped for hot water and city water because some products respond better to a cold-water rinse. The city water and purified water are controlled to within 1% of the set point. The other key utilities—steam (40 bar) and chilled water—are controlled within a range of 5% around these values. Heating and cooling of the system are kept to within +/- 3°C of the set point. A clean compressed air pipe to the system controls the operation of multiple valves. The dosing of water is controlled within a 1% v/v cleaning solution range. Steam pressure is at 40 bar, and the chilled water temp is controlled within a 5% range of this.

Process Equipment Design Review

The pilot system has numerous capabilities within the primary operations of mixing, heating, cooling, induction, pressure, vacuum, and CIP. The main vessel for primary mixing and an auxiliary vessel for additional product phases or premixes are made of 316 SS with a specified roughness (RA) finish. The transfer from the auxiliary vessel to the main vessel can be done using a pump or a pressure differential between the tanks. The system has fixed piping except for the raw material induction, which uses flex hoses. The system was designed with sanitary fittings and gasket materials that are compatible with the cleaning chemistry.

The mixing elements consist of the central agitator, outer scrapers, and homogenizer, all of which provide the system's flow and shear characteristics. There is an additional short and long loop in this system to enable batch turnover. The short loop goes from the homogenizer to the vessel's bottom and the long loop enters about two-thirds of the way up the vessel. The induction ports for both the main vessel and phase vessel are located on the front panels.

From a capability standpoint, the phase vessel can induct liquids, powders, and pellets. The main vessel can induct via the liquid port (into the homogenizer well), the powder port (into the homogenizer well), and the bottom port (into the vessel bottom dome). This system can work in both manual mode (semi-auto) or automatic mode (auto). A batch recipe system allows creating programs for both batch making and CIP. The human–machine interface (HMI) is located on the floor level and the platform for ease of access and operation.

The CIP chemicals are added manually after the water is dosed. The homogenizer works as the pump for the system, circulating fluid to the spray balls. The phase vessel is fitted with two cascade-style spray balls, and the main vessel is fitted with four cascade-style spray balls and side spray jets. For the main vessel, the system controls the pressure to the spray balls via a set point with a maximum value of 2,500 mbar. The vessels were tested for spray coverage during the site acceptance test (SAT) using a riboflavin test. The flow through the secondary loops in the system, like the induction and transfer lines, is also controlled by the homogenizer speed and can be customized to ensure turbulent flow. During the development run, a borescope was used to inspect the lines to determine visual cleanliness. The internal walls and mixer blades were inspected visually using a flashlight.

Product and Equipment Grouping

Product and equipment grouping is carefully reviewed; a well-justified grouping strategy can reduce time, personnel resources,

Figure 1: Cleaning recipe process map.



and costs. Most of the mixing tanks are similar in design and function and are grouped. The product grouping or family is primarily based on the product chemistry. Risk ranking has the following factors included: solubility, toxicity, and hardest to clean. Product families A–H are listed next. This list is constantly reviewed when new products are commissioned into the production facility. The hardest-to-clean product from the risk ranking is defined. The residue characteristics after the dirty hold time and during the cleaning process are also considered in the risk ranking process. Different steps of the cleaning process are : Family A: surfactant systems; Family B: silicone–water systems; Family C: oil–water emulsions that needed heating; Family D: high wax anhydrous systems; Family E: high TiO_2 systems; Family F: oil–water emulsions with no heating; Family G: high clay and oxide systems; and Family H: carbomer systems.

Cleaning Process Map

The cleaning recipe will follow a preset series of steps whose critical process parameters vary according to the difficulties of the related product. Figure 1 shows the process map for these steps; Figures 2 and 3 show before and after cleaning.

Analytical Test Method Validation

It is important to note that if the product and detergent residue limits provided by the calculations are high, swabbing limits will default to the upper limit of the validated test methods. For this reason, it is vital to develop testing methods that suit the processes and are flexible enough to cover a broad, extensive range that includes the residue limits that result. Another way of assessing the need for test methods is whether the resulting limitations warrant swab testing, in which case, other overarching methods can be favored. A more holistic approach to testing for residues is total organic carbon (TOC) testing if purified water is available. TOC testing can be much more reliable and sensitive for products containing organic carbon forms and is widely used in the biopharmaceutical industry.

Figure 2: Product residue before initial cleaning step.



Figure 3: Product residue after initial cleaning step.



A risk-based matrix approach can be used to determine the worst-case product for each cleaning procedure.

Residue Limits

Topical drug and cosmetic products represent some of the hardest-to-clean formulations. Additionally, it is important to keep in mind the level of toxicity of these formulations. Toxicity levels and acceptable degrees of residue buildup within the system are two of the most critical drivers for assessing acceptable limits. The low toxicity of most over-the-counter active ingredients makes their impact in the development process negligible, as represented by sunscreen actives and salicylic acid. As is the case of a product whose API is not significant, the carryover concern larger risk is attributed to product buildup.

Visual Inspection

Of all the active ingredients, raw materials, and detergents used within the manufacturing facility, the alkaline cleaning detergent has the highest reported toxicity, with a permitted daily exposure (PDE) value of 7 mg/day. A PDE of this level of toxicity in consumer products results in acceptable residue limit calculations in the tens of thousands, making the visual inspection a key element in the validation process. Current literature suggests that most solid residues can be visually detected at levels of 4 µg/cm² or less, making this method the most cost-effective tool in the topical drug and cosmetic cleaning process arsenal [9, 10].

Operations Partnership

Process control, training, and awareness are key elements to any successful cleaning program. Implementing a new program within a site that is manufacturing topical drugs and cosmetics requires continuous training and personnel assessment to ensure that all controls are successfully maintained. Controls tying product formulations to cleaning recipes are vital because equipment damage—rather than product contamination—is a greater concern with cleaning low-toxicity formulations.

CLEANING PROCESS VALIDATION

Cleaning Validation Master Plan

A cleaning validation master plan should be developed during the process development phase to guide the validation process, much like it is used for product process validation. This plan should contain, at a minimum, guidance on the following topics:

- Equipment description and system boundaries
- Product family descriptions and related cleaning processes
- Risk assessment and rationale for family groupings
- Resulting validation strategy, sampling site designation, and execution requirements
- Test method validation references

Residue limit calculations can be included in this document if the strategy focuses on a holistic set of calculations.

Product Risk Assessment

A risk-based matrix approach can be used to determine the worst-case product for each cleaning procedure. This approach considers the categories of risk factors such as ease of cleaning, solubility, toxicity, and concentration of active ingredients. Each product is rated per category according to these criteria, and each criterion has a range that defines the associated level of risk (none, low, medium, or high). Each risk factor category is assigned a multiplier that provides weighting based on the factor's criticality to the outcome of the cleaning process.

This assessment should be done per each product family and should be specific to the system geometry in which the cleaning process is to be executed because the cleanability of a product can vary substantially based on equipment capabilities.

System Readiness

Within a new facility, it is optimal to complete cleaning process validation alongside production process validation. This will ensure that all equipment is qualified and ready for use, as well as that no regulated products are released without first having an associated and assessed cleaning process in place. At this point, standard operating procedures should be established because of the initial development, production, and cleaning processes. Triaging parts and chemicals, manual processes, and CIP processes should have a base standard that can be reviewed as needed during and after the validation process.

Before going into a process validation phase, it is strongly advised to have first observed several runs of worst-case products. The validation stage includes successfully executing validation protocols that meet predetermined acceptance criteria. Returning to a development process within the execution of a validation protocol can come with complexities in documentation and regulatory compliance.

CONTINUED PROCESS VERIFICATION

Each cleaning procedure should be verified at least once every three years, or as determined by site policies, to ensure consistency and repeatability and to identify any issues that may be trending the process out of control before product contamination or finished good failures happen. The trending of critical parameters—such as cleaning agent concentration, cleaning time and temperature, and rinse water conductivity—is an important element of continued verification of the cleaning process. Each verification should be conducted in the same fashion as the previous validation process. An exception to this

is when process updates are desired. A draft of these updates should be provided with the validation documentation and implemented upon successful execution.

CONCLUSION

The nature and quantity of topical drug and cosmetic products manufactured onsite and the desire to have a compliant, lean, and efficient cleaning strategy warrant a structured approach to cleaning. Implementing a cleaning life-cycle approach with attention to the design phase, including lab studies and field trials, enabled the grouping of hundreds of products based on formulation characteristics. The field trials also incorporated visual inspection, TOC, and microbial surface testing. These results were analyzed and leveraged to reduce the testing scheme during the validation and monitoring phases. Understanding the equipment design, spray coverage, flow dynamics, heating ramp rates, rinse, and drying conditions is critical to optimize field trials and improve the laboratory test model. The result is a validated cleaning process based on a scientific, risk-based approach for a wide range of products and the ability to quickly evaluate and place new product formulations within an appropriate cleaning family.

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About the authors

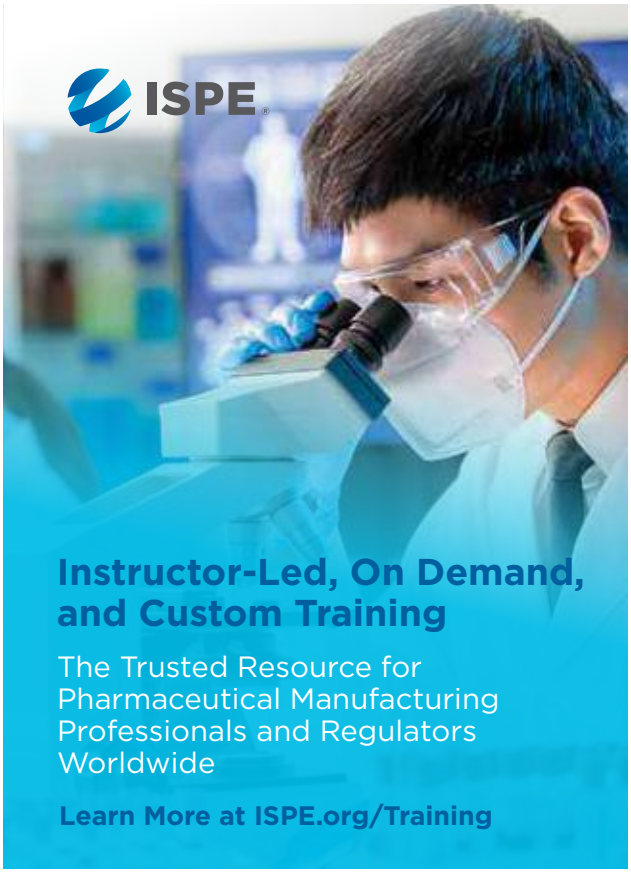
Dijana Hadziselimovic is a Technical Services Laboratory Specialist for the life sciences division of STERIS. She provides technical support in process and research cleaners, conducts laboratory experiments to recommend cleaning procedures, and provides field support. Dijana has over 20 years of laboratory experience in the pharmaceutical and biotech industries. She holds a BA in chemistry from the University of Missouri, St. Louis. She is active in the St. Louis Society of Cosmetic Chemists.

Kamini Rao, PhD, LSSBB, has a PhD in chemical engineering and over 20 years of experience in R&D, plant engineering, process engineering, product commercialization, and project management. She received her bachelor's degree from the Indian Institute of Technology, Kharagpur, and her advanced degrees from the University of Virginia, Charlottesville. She works for Bowery, a start-up in vertical farming, as a Senior Project Manager for their build and launch team.

Nicole Granda Alvarez is a Principal Engineer for extra-ocular devices in the chemistry and materials group of Alcon R&D Laboratories. She holds a bachelor's degree in environmental design and a master's degree in architecture from the University of Puerto Rico. Nicole has over a decade of experience in the regulatory industry in process engineering, quality, and validation with companies including Allergan, Johnson & Johnson, Abbott, Novartis, and Bristol Myers Squibb. She has experience as an architectural designer and LEED-accredited professional, and has volunteered in nonprofit organizations such as the US Green Building Council (USGBC) and ISPE.

Paul Lopolito is a Technical Services Senior Manager for the life sciences division of STERIS Corporation. He provides global technical support related to critical environment and process research cleaners, which includes field support, site audits, training presentations, and educational seminars. Paul has over 25 years of industry experience and has held positions as a technical services manager, manufacturing manager, and laboratory manager. He has been an ISPE member since 2012.

Steven Robbins is an Account Manager for the STERIS life science contamination control solutions group. Steve has over 20 years of technical support experience in the pharmaceutical and regulated life science industry. His career has been focused on supporting cleaning and bioburden control, including cleaning cycle development, clean-in-place systems, equipment design, environmental sustainability, cleanroom control, and sterility assurance. Steve holds a BS in manufacturing and industrial management and an AAS in electrical engineering. He has been an ISPE member since 2012.



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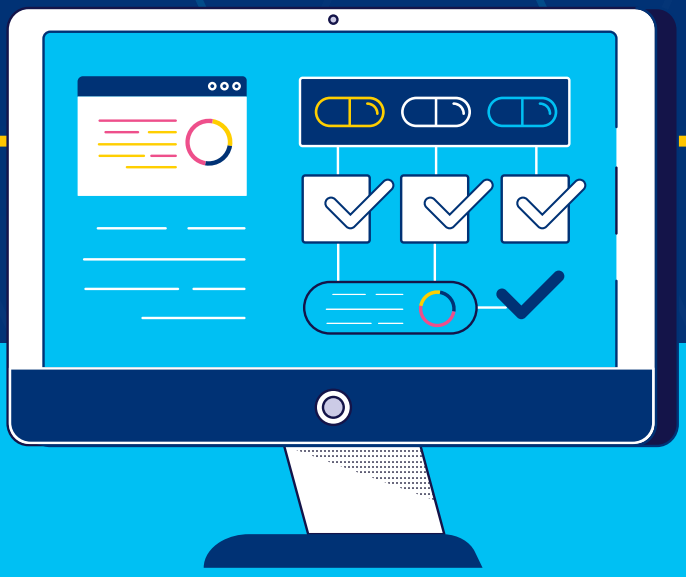

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